“THE PREVALENCE OF METABOLIC SYNDROME IN YOUNG ACUTE CORONARY SYNDROME PATIENTS”

A DISSERTATION SUBMITTED TO THE TAMILNADU
Dr. MGR MEDICAL UNIVERSITY

CHENNAI

In partial fulfilment of the Regulations

for the award of the Degree of

DOCTOR OF MEDICINE – BRANCH I GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE
TIRUNELVELI MEDICAL COLLEGE
TIRUNELVELI

MAY 2018

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled**"THE PREVALENCE OF METABOLIC SYNDROME IN YOUNG ACUTE CORONARY SYNDROME PATIENTS "** is a bonafide research work done by **Dr. JERRY ABRAHAM JOSEPH**, Postgraduate Student in Department of General Medicine, Tirunelveli Medical College & Hospital, Tirunelveli, in partial fulfilment of the requirement for the degree of M.D., in GENERAL MEDICINE

Prof.Dr.ARUMUGAPANDIAN.S.MOHAN.M.D.,
Professor & Head of Department,
Department of General Medicine,
Tirunelveli Medical College,
Tirunelveli

Date:
Place: Tirunelveli

CERTIFICATE BY THE HEAD OF DEPARTMENT

This is to certify that the dissertation entitled **"THE PREVALENCE OF METABOLIC SYNDROME IN YOUNG ACUTE CORONARY SYNDROME PATIENTS"** is a bonafide research work done by **Dr. JERRY ABRAHAM JOSEPH**, Postgraduate M.D. student in Department of General Medicine, Tirunelveli Medical College & Hospital, Tirunelveli, under the guidance of **Prof.Dr.ARUMUGAPANDIAN S.MOHAN,** Professor & Head of department , Department of Medicine,Tirunelveli Medical College & Hospital, Tirunelveli, in partial fulfilment of the requirements for the degree of M.D. in GENERAL MEDICINE.

Date:
Place:Tirunelveli

Prof.Dr.ARUMUGAPANDIAN S.MOHAN.M.D.,
Professor and HOD of General Medicine,
Department of General Medicine,
Tirunelveli Medical College,

CERTIFICATE BY THE HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"THE PREVALENCE OF METABOLIC SYNDROME IN YOUNG ACUTE CORONARY SYNDROME PATIENTS"** is a bonafide and genuine research work carried out by **Dr. JERRY ABRAHAM JOSEPH** under the guidance of Prof.**Dr.ARUMUGAPANDIAN.S.MOHAN,M.D.,** Professor & Head of Department, Department of General Medicine , Tirunelveli Medical College, Tirunelveli.

Date:
Place: Tirunelveli

Dr.K.Sithy Athiya Munavarah,MD., (Patho)
DEAN
Tirunelveli Medical College,
Tirunelveli

COPYRIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that dissertation entitled **"THE PREVALENCE OF METABOLIC SYNDROME IN YOUNG ACUTE CORONARY SYNDROME PATIENTS''** is a bonafide and genuine research work carried out by me under the guidance of Prof. **Dr.ARUMUGAPANDIAN. S. MOHAN, M.D.,** Professor & Head of Department, Department of General Medicine, Tirunelveli Medical College, Tirunelveli.

The Tamil Nadu Dr.M.G.R. Medical University,Chennai shall have the rights to preserve, use and disseminate this dissertation in print or electronic format for academic/research purpose.

Date:
Place: Tirunelveli

Dr.Jerry Abraham Joseph. MBBS.,
Postgraduate in General Medicine,
Department of General Medicine,
Tirunelveli Medical College,
Tirunelveli

ACKNOWLEDGEMENT

I am obliged to record my immense gratitude to **Dr.Sithy Athiya Munavarah.M.D.,** Dean, Tirunelveli Medical College Hospital for providing all the facilities to conduct the study.

I express my deep sense of gratitude and indebtedness to my respected Professor and guide Prof. **Dr. ARUMUGAPANDIAN. S. MOHAN, M.D.,** Professor and Head of Department, Department of General Medicine, Tirunelveli Medical College, Tirunelveli, whose valuable guidance and constant help have gone a long way in the preparation of this dissertation.

I am also thankful to my Assistant Professors **Dr.R.PERIYASAMY.M.D., Dr.A.RAJESH.M.D., Dr.MARCHWIN KINGSTON.M.D., Dr.S.M.SHAVANA M.D.,** and **Dr.MADHAVAN,M.D.,** for their help.

I offer my special thanks to Prof. **Dr.J. M. RAVICHANDRAN EDWIN M.D D.M**., Professor & Head of Department, Department of cardiology for kind co-operation and valuable guidance.

I express my thanks to all Professors, Associate Professors, Assistant Professors, Staff members of the Department of General Medicine and all my Postgraduates colleagues, C.R.R.I s and friends for their help during my study and preparation of this dissertation and also for their co-operation.

I wish to acknowledge my parents and family members for their everlasting blessings and encouragement.

I thank all my patients who participated in this study for their extreme patience and kind co-operation.

Above all I thank the Lord Almighty for his kindness and benevolence.

Date:
Place: Tirunelveli

Dr. JERRY ABRAHAM JOSEPH.MBBS.,
Postgraduate in General Medicine,
Department of General Medicine,
Tirunelveli Medical College,
Tirunelveli

CONTENTS

TIRUNELVELI MEDICAL COLLEGE

INSTITUTIONAL RESEARCH ETHICS COMMITTEE
TIRUNELVELI, STATE OF TAMILNADU, SOUTH INDIA PIN 627011
91-462-2572730-EXT: 91-462-2572944; 91-462-2579785; 91-462-2572611-16
online@tvmc.ac.in, irec@tvmc.ac.in, www.tvmc.ac.in

CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC REF NO:861/GM/2016

PROTOCOL TITLE: THE PREVALENCE OF METABOLIC SYNDROME IN YOUNG ACUTE CORONARY SYNDROME PATIENTS

PRINCIPAL INVESTIGATOR: Dr. JERRY ABRAHAM JOSEPH, MBBS

DESIGNATION OF PRINCIPAL INVESTIGATOR: POST GRADUATE IN GENRAL MEDICINE

DEPARTMENT & INSTITUTION: TIRUNELVELI MEDICAL COLLEGE, TIRUNELVELI

Dear , Dr. Jerry Abraham, MBBS.,, The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 05.08.2016.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☐
2.	Study Protocol	☐
3.	Department Research Committee Approval	☐
4.	Patient Information Document and Consent Form in English and Vernacular Language	☐
5.	Investigator's Brochure	☐
6.	Proposed Methods for Patient Accrual Proposed	☐
7.	Curriculum Vitae of the Principal Investigator	☐
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☐
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/ Material Transfer Agreement (MTA)	☐
14.	Clinical Trials Registry-India (CTRI) Registration	☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should rebeive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in the protocol must be informed.

STANDS APPROVED UNDER SEAL

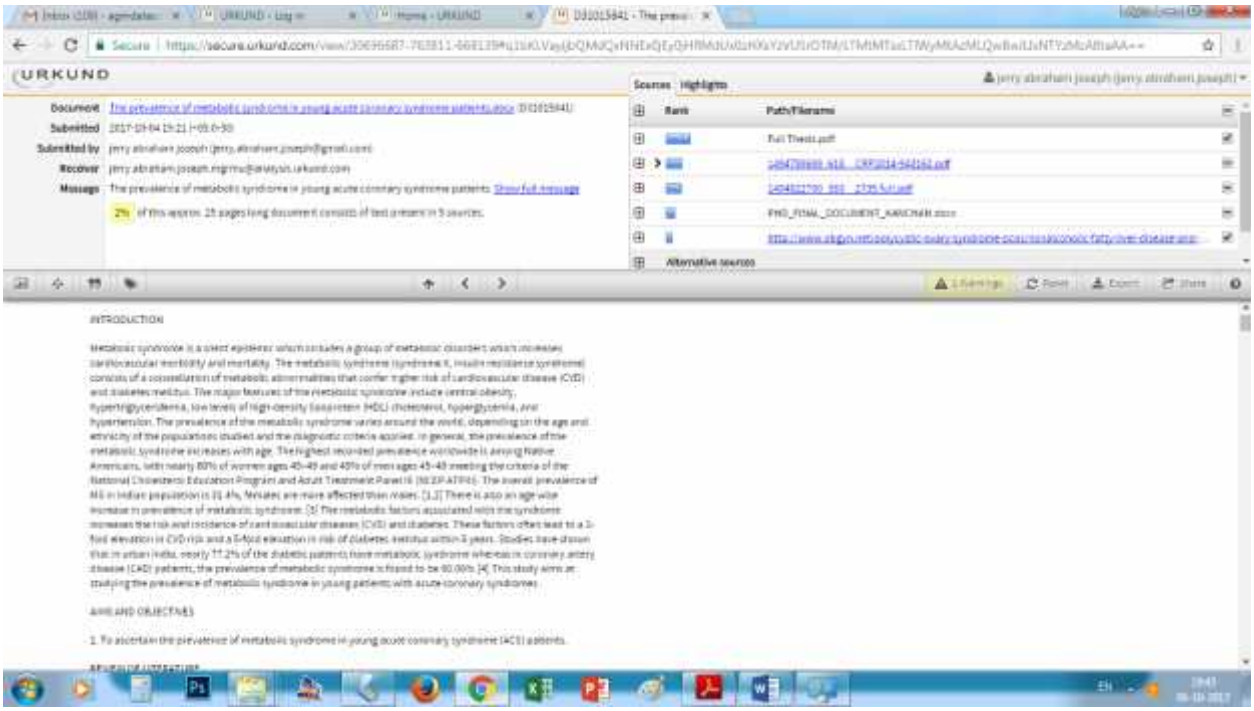
Dr.K.Shantarasan MD
Registrar, TIREC
Tirunelveli Medical College, Tirunelveli - 627011
State of Tamilnadu, South India

Dr.J.Suresh Durai, MD
Member Secretary, TIREC
Tirunelveli Medical College, Tirunelveli - 627011
State of Tamilnadu, South India

CERTIFICATE - II

This is certify that this dissertation work title **"THE PREVALENCE OF METABOLIC SYNDROME IN YOUNG ACUTE CORONARY SYNDROME PATIENTS"** of the candidate **Dr. JERRY ABRAHAM JOSEPH** with registration Number **201511353** for the award of M.D.in the branch of **MEDICINE.** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows **2 percentage** of plagiarism in the dissertation.

Guide & Supervisor sign with Seal.


URKUND
Document
Submitted
Submitted by
Receiver
Message
Sources
Highlights
Path/Filename
Alternative sources
INTRODUCTION
AIMS AND OBJECTIVES
1. To ascertain the prevalence of metabolic syndrome in young acute coronary syndrome (ACS) patients.

INTRODUCTION

Metabolic syndrome is a silent epidemic which includes a group of metabolic disorders which increases cardiovascular morbidity and mortality. The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer higher risk of cardiovascular disease(CVD) and diabetes mellitus. The major features of the metabolic syndrome include central obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, hyperglycemia, and hypertension. The prevalence of the metabolic syndrome varies around the world, depending on the age and ethnicity of the populations studied and the diagnostic criteria applied.

In general, the prevalence of the metabolic syndrome increases with age. The highest recorded prevalence worldwide is among native americans, with nearly 60% of women of age 45–49 and 45% of men of age 45–49 meeting the criteria of the National Cholesterol Education Program and Adult Treatment Panel III (NCEP:ATPIII).

The overall prevalence of MS in Indian population is 31.4%, females are more affected than males.[1,2]There is also an age wise increase in prevalence of metabolic syndrome.[3]The metabolic factors associated with the syndrome increase the risk and incidence of cardiovascular diseases(CVD) and diabetes. These factors often lead to a 2-fold elevation in CVD risk and a 5-fold elevation in risk of diabetes mellitus within 5 years. Studies have shown that in urban

India, nearly 77.2% of the diabetic patients have metabolic syndrome whereas in coronary artery disease (CAD) patients, the prevalence of metabolic syndrome is found to be 60.06%.[4]This study aims at studying the prevalence of metabolic syndrome in young patients with acute coronary syndromes.

AIMS AND OBJECTIVES

1. To ascertain the prevalence of metabolic syndrome in young acute coronary syndrome (ACS) patients.

REVIEW OF LITERATURE

The metabolic syndrome is a constellation of metabolic abnormalities that are seen in patients, which increases the risk of cardiovascular abnormalities.It has previously been known by several other names, including SyndromeX , Reaven's syndrome, the DeadlyQuartet, and the more pathophysiologic term, insulin resistancesyndrome. The components of the metabolic syndrome are abdominal obesity, dyslipidemias (hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol), hypertension, insulin resistance, prothrombotic and proinflammatory states.The role of metabolic syndrome in causing increased risk of cardio vascular diseases has been a topic of debate. The studies suggest that the individual parameters of metabolic syndrome interdigitate in a way that it worsens the prognostic outcomes more than what would be expected from a single risk factor.

DEFINING METABOLIC SYNDROME

The earliest awareness about metabolic syndrome in patients with clustering of various metabolic abnormalities was as early as 1923 but it was much later, in 1988, Reaven coined the term 'syndrome X' for this entity.[5]More than 80 years ago, Kylin described the clustering of diabetes, gout, and hypertension in individuals. In the mid–20th century, French physician Dr. Jean Vague made the observation that upper body obesity appeared to predispose to type 2 diabetes mellitus and heart disease,

whereas lower body obesity did not have those associations. He obsvered that a “male” pattern of body fat distribution, which he referred to as android obesity, was more likely to be associated with diabetes and cardiovascular disease (CVD). The concept of insulin resistance as underlying a cluster of risk factors originated with Dr. Gerald Raeven in 1988. Insulin resistance syndrome or syndrome X was originally described in lean individuals.

The last two decades have brought forth a number of definitions and criteria to identify this condition. Raeven’s definition included components like resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, increased plasma levels of very-low-density lipoprotein–triglyceride(VLDL-TG), decreased plasma high-density lipoprotein cholesterol(HDL-C) concentration, and hypertension. He attributed the aetiology of this cluster of risk factors to the presence of insulin resistance (IR).

A working definition of metabolic syndrome (MS) was proposed by WHO,[6]in 1999, which was modified afterwards multiple times. WHO defined metabolic syndrome as glucose intolerance, impaired glucose tolerance (IGT) or diabetes mellitus (DM), and/ or insulin resistance, together with two or more of the components listed below:

1. Raised arterial pressure, i.e., ≥140/90 mm of Hg

2. Raised plasma triglyceride (≥ 150 mg/dl) and/or low HDL-C (<35 mg/dl in men and <39 mg/dl in women)

3. Central obesity, i.e., waist/hip ratio (WHR) >0.9 in men and >0.85 in women and/or body mass index (BMI) >30 kg/m2

4. Microalbuminuria, i.e., urinary albumin excretion rate ≥ 20 μgm/min or albumin/creatine ratio ≥ 30 μgm/mg.

European Group For Study Of Insulin Resistance Definition [7]

The European Group for Study of Insulin Resistance (EGIR) did a modification of the WHO definition, using the term insulin resistance syndrome rather than MS. According to the EIGR definition the diagnostic criteria included elevated plasma insulin (>75th percentile) plus two other factors from among the following

1. Abdominal obesity: waist circumference (WC) ≥94 cm in men and ≥80 cm in women2. Hypertension: ≥140/90 mm of Hg or on antihypertensive treatment 3. Elevated triglycerides (≥150 mg/dl) and/or reduced HDL-C (<39 mg/dl for both men and women) 4. Elevated plasma glucose: impaired fasting glucose (IFG) or IGT, but no diabetes

EGIR gave more emphasis on abdominal obesity with respect to WHO, but EGIR excluded patients with type 2 DM from their syndrome because insulin resistance was viewed primarily as a risk factor for diabetes.

This definition was followed by a simpler definition released by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).[8]

NCEP:ATPIII 2001

Three or more of the following:

• Central obesity: waist circumference >102 cm (M), >88 cm (F)

• Hypertriglyceridemia: triglyceride level ≥150 mg/dL or specific medication

• Low HDL*c* cholesterol: <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication

• Hypertension: blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic or specific medication

• Fasting plasma glucose level ≥100 mg/dL or specific medication or previously diagnosed type 2 diabetes

Harmonizing Definition

Three of the following:

• Waist circumference (cm)

Men	Women	Ethnicity
≥94	≥80	Europid,Sub-Saharan African, Eastern And Middle Eastern
≥90	≥80	South Asian, Chinese and Ethnic South and Central American
≥85	≥90	Japanese

• Fasting triglyceride level >150 mg/dL or specific medication

• HDL cholesterol level <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication

• Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication

• Fasting plasma glucose level ≥100 mg/dL (alternative indication: drug treatment of elevated glucose levels)

EPIDEMIOLOGY

Metabolic syndrome is now considered as both a public health and a clinical problem. The prevalence of the metabolic syndrome varies around the world depending on the age and ethnicity of the populations [9] studied and the diagnostic criteria used in the evaluation. It has been demonstrated that the syndrome is common and that it has a rising prevalence worldwide, which related largely to increasing obesity and sedentary lifestyles. In general, the prevalence of the metabolic syndrome increases with age. The maximum prevalence worldwide is found to be among native americans, with nearly 45% of men of age 45–49 and 60% of women of age 45–49 meeting the criteria of the National Cholesterol Education Program and Adult Treatment Panel III (NCEP:ATPIII).The global industrialization is an important factor associated with rising rates of obesity, which are expected to increase the prevalence of the metabolic syndrome dramatically. Moreover, the rising prevalence and severity of obesity

among children is reflected in features of the metabolic syndrome in a younger population. Increase in waist circumference predominate among women. The parameters most commonly altered in men are increase in fasting plasma triglyceride levels (i.e., to >150 mg/dL), reductions in HDL cholesterol levels and hyperglycemia.

RISK FACTORS

Overweight/Obesity

Central adiposity is an important component of the syndrome. The prevalence of the syndrome shows the strong relationship between waist circumference and increasing adiposity. However, patients who are of normal weight may also be insulin resistant and can present with the metabolic syndrome. The Framingham Study showed that obesity was an independent risk factor for the incidence of cardiovascular disease in men and women which includes coronary artery disease, stroke, and congestive heart failure. The waist-to-hip ratio can be taken as an important predictor of the above mentioned risks. If the patient has additional risk factors like hypertension and glucose intolerance along with obesity, the adverse impact of obesity is even more evident. The effect of obesity on cardiovascular mortality in women may be seen at BMIs as low as 25. Obesity, especially abdominal obesity, is associated with an atherogenic lipid profile. The abnormalities usually noticed include elevated low-density lipoprotein cholesterol, very-low-density lipoprotein, and

triglyceride. The high-density lipoprotein cholesterol is lowered. The vascular protective molecules like adipokine, adiponectin are seen in lower levels.

Sedentary Lifestyle

Physical inactivity can be considered as a risk factor cardiovascular disease and the related risk of death. Most of the factors in the metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central), reduced HDL cholesterol, and increased triglycerides, blood pressure, and glucose in genetically susceptible persons.

Aging

The metabolic syndrome affects nearly 50% of the U.S. population older than age 50, and at >60 years of age women are more often affected than men. The age dependency of the syndrome's prevalence is seen in most populations around the world.

ETIOLOGY AND PATHOPHYSIOLOGY

The underlying pathogenesis of the metabolic syndrome remains incompletely understood. Obesity and insulin resistance are two of the most commonly proposed conditions that lead to the other metabolic

derangements. Abdominal obesity is a measure of visceral adiposity. Visceral adipose tissue is particularly active as an endocrine organ and produces fatty acids, tumor necrosis factor (TNFa), components of the renin-angiotensin-aldosterone cascade, plasminogen activator inhibitor (PAI-1), and adiponectin. These adipose tissue products can contribute to insulin resistance, hypertension, proinflammatory and procoagulable states. Insulin resistance is also felt to play a central role, yet its contribution to the other criteria remains poorly defined.

Role of Insulin resistance

Insulin action: The insulin is one among the potent anabolic hormone which plays a significant role in glucose, fat and protein metabolism. It also helps in cellular growth, cellular differentiation and the endothelial function. The effects of insulin are mainly on three tissues; Liver, Muscle and Adipose tissue.

The mechanism of action of insulin involves autophosphorylation and phosphorylation of intracellular substrates at the insulin receptor level. Insulin receptor transphosphorylation of insulin receptor substrate (IRS) proteins (1-4) leads to the activation of downstream signaling pathways which mediate insulin actions with IRS -1 playing a prominent role in the skeletal muscle and IRS-2 in the liver. The two major signaling pathways activated by insulin binding to its receptor

are the phosphatidylinositol -3 kinase (PI3K) pathway and mitogenic or mitogen-activated protein kinase (MAPK) pathway.

The major metabolic actions insulin like glycogen, lipid and protein synthesis, vasodilatation and anti-inflammatory effects are mediated by PI3K pathway. This pathway is involved in glucose transporters (GLUT4) translocation, resulting in increased insulin mediated glucose uptake by adipose tissue and muscle. The MARK pathway activation is related with actions of insulin like cell growth and proliferation. The MARK pathway also plays a role in decreased nitric oxide production and procoagulant effects.

Insulin resistance:

Insulin resistance is defined as a subnormal /decreased biologic response to a given concentration of insulin. Although insulin effects are pleiotropic in nature, the term ‘insulin resistance’ typically denotes the actions of insulin on glucose metabolism. [10]The onset of insulin resistance is characterised by postprandial hyperinsulinemia, which is followed by fasting hyperinsulinemia and ultimately by hyperglycemia. An increased level of circulating fatty acids is major contributor to the development of insulin resistance in early stages. The action of lipolytic

enzymes releases plasma albumin-bound free fatty acids predominantly from adipose-tissue triglyceride stores.. Fatty acids are also derived from the lipolysis of triglyceride rich lipoproteins in tissues by lipoprotein lipase. The mechanism of action of insulin includes both antilipolysis and the stimulation of lipoprotein lipase in adiposetissue. The most important action of insulin is the inhibition of lipolysis in adipose tissue.When a patient develops insulin resistance, increased lipolysis occurs resulting in more fatty acids production , which further decrease the antilipolytic effect of insulin. Excessive fatty acids enhance substrate availability and create insulin resistance by modifying downstream signalling. Fatty acids impair insulin-mediated glucose uptake and accumulate as triglycerides in both skeletal and cardiac muscle, whereas increased glucose production and triglyceride accumulation take place in the liver.

Another factor resulting in development of insulin resistance, hyperlipidemia, and cardiovascular disorders is Leptin resistance. In a normal human body leptin exerts its physiological actions. It reduces appetite, promotes energy expenditure, and enhances insulin sensitivity. Leptin may also play a role in regulating regulate cardiac and vascular function through a nitric oxide dependent mechanism. When a patient develops obesity, hyperleptinemia occurs resulting in inflammation, insulin

resistance, hyperlipidemia, and adverse cardiovascular effects such as hypertension, atherosclerosis, CHD and finally heart failure.

Primary and secondary insulin resistance

Intrinsic (primary) defects in insulin sensitivity due to mutations affecting any protein between the receptor and the final insulin-regulated proteins. Insulin resistance of the metabolic syndrome results from impairments in cellular events distal to the interaction between insulin and its surface receptor.

The secondary resistance is defined by the restoration of normal insulin sensitivity after the removal of the factor or state. Glucocorticoids, glucagon, catecholamine, and growth hormone induce insulin resistance in cases of the excess secretion of individual hormones. The resistance to action of insulin is further increased in presence of infection and stress. Another important secondary factor that can affect the sensitivity of target cells to insulin is spontaneously occurring antibodies to the insulin receptor. Such antibodies are typically polyclonal IgG . These typically develop in the presence of other autoimmune disorders. The receptor binding of antibodies impairs the action of insulin.

Type A and Type B resistance

The inherited syndromes of severe insulin resistance constitute the type A syndrome of insulin resistance. It is characterized by marked endogenous hyperinsulinemia with or without glucose intolerance, acanthosis nigricans, and in affected post pubertal women, ovarian hyperandrogenism. Leprechaunism and Lipodystrophy are classical examples.

Type B resistance is due to antibodies to insulin receptor which may be associated with other autoimmune diseases.

Insulin Resistance And Hypertension

Studies have shown that there is an elevation of systolic blood pressure of 1.7 mm Hg and diastolic blood pressure of 2.3 mm Hg for each 10 unit increase in insulin resistance (10 M/min per Kilogram decrement in molar value). The proposed mechanisms by which insulin resistance and hyperinsulinemia contribute to the pathogenesis of hypertension include; activation of the sympathetic nervous system, increased activity of the Na/ H exchange pump, increased retention of renal sodium, and increased salt sensitivity .Vasodilatory action of insulin is lost in resistant state.

Increased Waist Circumference

Waist circumference is considered one among the required component of the latest and commonly applied diagnostic criteria for the metabolic syndrome. Excess abdominal fat, which can be assessed by measurement of waist circumference or waist-to-hip ratio, is found to be associated with a higher risk for diabetes mellitus and cardiovascular disease. The waist circumference assessment can be considered as an alternative for visceral adipose tissue. The measurement of waist circumference should be performed in the horizontal plane above the iliac crest. The method of waist circumference measurement does not reliably distinguish between SC adipose tissue and visceral fat. The correct assessment can be made only with the help of CT or MRI. Visceral fat, when compared with the subcutaneous tissue, represents a metabolically active organ strongly related to insulin sensitivity. Adipocytes form visceral fat has very much alterted property when compared to adipocytes in subcutaneous fat. It is mainly composed of large, insulin resistant adipocytes and also has well organized blood vessel network with the infiltration of inflammatory cells. When the amount of visceral adipose tissue increases, free fattyacids derived from the adipose tissue– are directed to the liver. But in increased abdominal subcutaneous tissue, lipolysis products are released into the systemic circulation and produces decreased direct effects on hepatic metabolism. Relative increase in visceral versus subcutaneous adipose tissue with increasing waist circumference in Asians and Asian Indians

may explain the greater prevalence of the syndrome in those populations than in African-American men, in whom SC fat predominates.

Obesity has been thought of occurring due to a sedentary lifestyle and long duration consumption of excess calories. The genetic influences play a role in about 40–70% of obesity. Genetic studies have identified about five genes affecting control of appetite in mice. Mutations of each gene result in obesity, and each has a human homolog. One gene codes for a protein expressed by adipose tissue known as leptin and another for the leptin receptor in the brain. The other three genes affect brain pathways downstream from the leptin receptor. Numerous other candidate genes for human obesity have been identified. Only a small percentage of human obesity is thought to be due to single gene mutations. Most human obesity undoubtedly develops from the interactions of multiple genes, environmental factors, and behaviour. The rapid increase in obesity in the last several decades clearly points to major roles for environmental and behavioural factors in the pathogenesis of obesity

TNF α and adiponectin are the two important hormones secreted by visceral adipose tissue appears to play key roles in generation of metabolic syndrome. The expression of TNF α is increased during weight gain and reduced with weight loss. TNF α and adiponectin are antagonistic in stimulating nuclear transcription factor – KB (NF – KB) activation.TNF α induces oxidative stress, which leads to dyslipidaemia,

glucose intolerance, insulin resistance, hypertension, endothelial dysfunction, and atherogenesis.

The activation of NF–KB leads to the formation of inflammatory cytokines, along with adhesion molecules thus promoting endothelial dysfunction. Elevated free fatty acid, glucose, and insulin levels enhance NF–KB activation and further results in specific clinical manifestations of metabolic syndrome. [11]

The features of emerging Asian Indian phenotype is High body fat with relatively less body BMI, Less lean body mass (Particularly in lower limbs), High BF/ BMI ratio (Higher body fat per unit BMI), high waist – hip ratio, variable subscapular / triceps ration, high intramyocellular lipids.[12]Thus asian metabolic syndrome is the constellation of adverse metabolic and clinical effects of insulin resistance.

Dyslipidemia

Hypertriglyceridemia denotes high blood levels of triglycerides, the most abundant fatty molecule in most organisms. Elevated levels of triglycerides arepredispose to atherosclerosis even if total cholesterol levels are normal and may result in coronary artery diseases. Pancreatitis risk is also high in the presence of high triglyceride levels. The elevation of triglycerides is a characteristic of lipid panel in diabetes and constitute an independent risk

factor for CAD. Hypertriglyceridemia also correlates with abdominal obesity.High carbohydrate diet, high fat diet, obesity and insulin resistance are major risk factors of hypertriglyceridemia. A potent independent relationship exists between CVD and triglyceride (TG) level, which is present in insulin resistance and metabolic syndrome and particularly in women and elderly patients. CVD event rates are twice as high in patients with TG more than 200 mg/dl compared with those with normal TG levels. Controversy continues over whether elevated TG levels directly influence plaque formation and stability or whether TG levels are more a marker of other comorbid conditions that contribute to the development of atherosclerotic disease.

Apart from triglyceride abnormality, the other major lipoprotein anomaly in patients the metabolic syndrome is a reduction in HDL cholesterol. This reduction occurs due to changes in HDL composition and metabolism. There occurs reduced cholesteryl ester content of the lipoprotein core and the particle become small and dense. The change in lipoprotein composition leads to increased clearance of HDL. These variations occurring in HDL metabolism is mostly indirect and occurs in presence of changes in triglyceride metabolism in context of insulin resistance.

The low-density lipoproteins(LDLs) are also modified in composition in the metabolic syndrome. In patients with metabolic syndrome there is predominance of small, dense LDLs, which are thought to be more atherogenic than normal LDL. The predominance of small dense LDL occurs especially when the levels of triglycerides at >2.0mM (~180 mg/dL). Since the presence of small dense LDL occurs with the presence of associated hypertriglyceridemia and low HDLs, independent contribution to CVD events difficult to predict. Individuals with hypertriglyceridemia often have increase in cholesterol content of both VLDL1and VLDL2 subfractions and in LDL particle number. Both of these lipoprotein changes may contribute to atherogenic risk in patients with the metabolic syndrome.

Role of free fatty acids

The body utilises the FFAs as an alternate fuel to glucose. The hormone-sensitive lipase acts on adipose cell to release free fatty acids. In the setting of insulin resistance, decreased insulin activity stimulates hormone sensitive lipase. An increased level of FFA has effect on liver and skeletal muscle. In liver, it enhances FFA oxidation, which is a powerful stimulus to gluconeogenesis. In skeletal muscle, glucose use is inhibited as FFA oxidation increases with the higher FFA levels. The effect insulin resistance in muscle leads to impairment of both glucose oxidation and

glucose storage. Some studies have shown that the intracellular fatty acid metabolites like diacylglycerol, fatty acyl CoAs, or ceramides activate a serine / threonine kinase cascade . The activation of cascade leads to phosphorylation of serine/ threonine sites on insulin receptors. The serine phosphorylated sites fail to activate PI3 kinase resulting in decreased glucose transport. In parallel to the decreased glucose transport due to increased FFA, there is enhanced gluconeogenesis and hepatic glucose production. Thus, when the skeletal muscle is taking up less glucose, the liver is producing more glucose, leading to increased glucose levels.

Role of fructose consumption

Fructose is one among the potent inducer of hepatic lipogenesis.[13] Fructose excess results in hepatic lipogenesis and over production of TG-rich VLDL particles. This leads to increased fat content of adipocytes. There occurs the increased fat secretion from adipocytes and dysregulated productionof adipokines.[13] TNFalpha activates JNK-1, a kinase that involved in inhibitory serine phosphorylation of IRS – 1 in adipose tissue and the liver.

Coagulation abnormalities

Fibrinogen plasminogen activator inhibitor-1(PAI-1) is one of the important regulator of fibrinolysis .The increased levels decreases the

fibrinolytic activity, by which it enhances the risk for clot formation. In patients with metabolic syndrome function of platelet is s also affected. There is enhanced aggregation of platelets. A wide variety of abnormalities of vascular function are associated with insulin resistance and the metabolic syndrome. The major mechanisms associated with vascular abnormality may include resistance to insulin mediated vasodilatation, abnormal endothelial signalling, and increased sympathetic nervous system activity. Also reduced release and responsiveness to nitric oxide, a potent vasodilator derived from endothelial cells, may also have a role on the pathogenesis.

Role of adipocytokines

Adiponectin

Adiponectin is one of the most important inflammatory marker associated with metabolic syndrome.[14]In patients with metabolic syndrome , adiponectin level are lowered. It is also seen in decreased levels in patients with diabetes mellitus and coronary artery disease patients. The levels of adiponectin correlate inversely with inflammation and hsCRP levels. Adiponectin has multiple actions like enchanced insulin sensitivity resulting in anti diabetic and anti atherogenic effects. The other major actions include decreased influx of non esterified fatty acids, reduced hepatic glucose output,inhibition of monocyte adhesion, macrophage

transformation to foam cells, and decreased proliferation on migrating smooth muscle cells. It also increases glucose and free fatty acid uptake by muscle.

Leptin

Leptin is an adipocytokine produced by subcutaneous adipose tissue. It is independently associated with increased risk of cardiovascular disease.

Monocyte chemoattractant protein -1

MCP-1 is involved in the recruitment of monocytes to the site of inflammation and thus it plays important role in atherosclerosis. The levels of MCP is elevated in patients with diabetes, insulin resistance and obesity

Resistin

Resistin is probably produced from adipose tissue. Increased levels of resistin is seen in patients with insulin resistance and obesity

Plasminogen activator inhibitor -1

PAI-1 is found in increased levels in patients with diabetes, obesity and metabolic syndrome. It is found that obese patients have increased adipose tissue PAI-1 mRNA and plasma PAI-1 protein levels when compared with lean adults.[15]

Interleukin -6

Il-6 is the most important among interleukins involved in inflammatory response. The levels of IL-6 show a positive correlation with insulin resistance. It is also elevated in patients with obesity and cardiovascular disease. The studies conducted in mouse models has shown that IL-6 acts by decreasing the activation of insulin receptor substrate 1 (IRS1) and PI3 kinase. It also impairs glycogenolysis in liver cells.

Other pro inflammatory cytokines

There are other cytokines involved in inflammation. The most important ones are IL-10, tumor necrosis factor (TNF), IL-1 and serum amyloid A (SAA)[16]

FIGURE 1

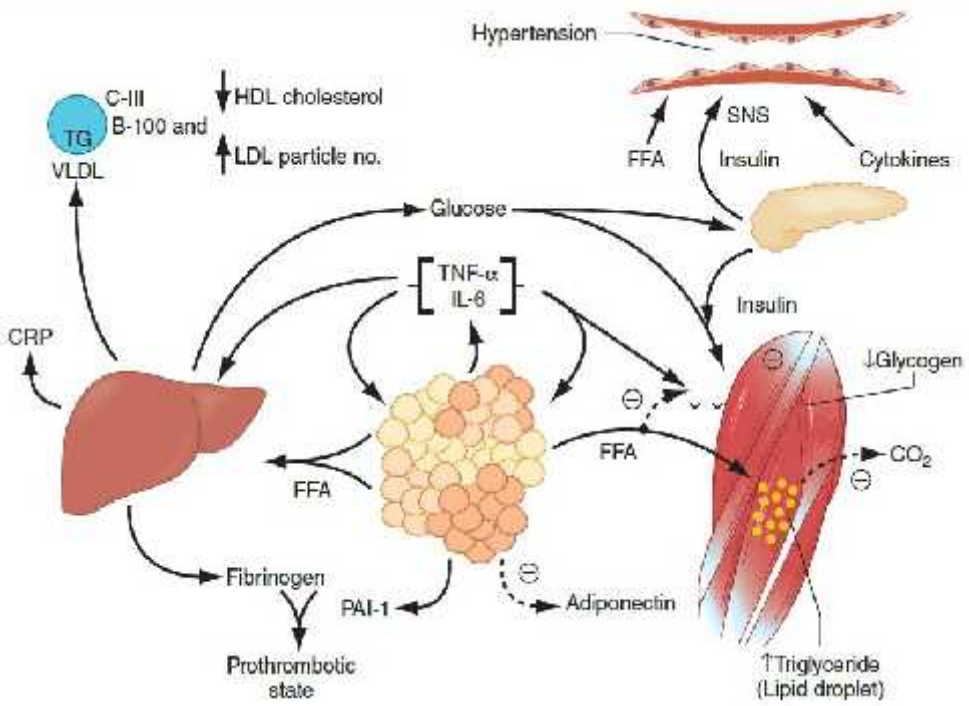


FIGURE 1: Free fatty acids (FFAs) are released in abundance from an expanded adipose tissue mass. In the liver, FFAs result in synthesis of glucose, triglycerides and VLDLs. Reductions in HDL cholesterol and an increased LDL particle number occurs. FFAs decreases insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation in triglyceride (TG).The elevated glucose, and to some extent FFAs, increases pancreatic insulin secretion, resulting in hyperinsulinemia. Hyperinsulinemia cause sodium reabsorption and increased sympathetic nervous system (SNS) activity and contribute to hypertension, as might higher levels of circulating FFAs. The proinflammatory state is superimposed and contributory to the insulin resistance produced by excessive FFAs. The enhanced secretion of IL-6 and TNFα produced by adipocytes and monocyte-derived macrophages results in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFAs. IL-6 and other cytokines also enhance hepatic glucose production, VLDL production by the liver, hypertension and insulin resistance in muscle. Cytokines and FFAs also increase hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor1 (PAI-1), resulting in a prothrombotic state. Higher levels of circulating cytokines stimulate hepatic production of C-reactive protein (CRP). Reduced production of the anti-inflammatory and insulin-

sensitizing cytokine adiponectin is also associated with the metabolic syndrome. [17]

CLINICAL FEATURES

Symptoms and Signs [18]

The metabolic syndrome is not characterised by any specific symptoms. The general examination of a patient may reveal increased abdominal circumference and elevated blood pressure. The presence of increased waist circumference or elevated blood pressure should be considered as a clue for the clinician to search for other biochemical abnormalities that may be associated with the metabolic syndrome. The other rare physical examination findings include lipoatrophy or acanthosis nigricans. Since the above mentioned physical findings characteristically are associated with severe insulin resistance, other components of the metabolic syndrome should be expected.

ASSOCIATED DISEASES

Cardiovascular disease

There is increased risk of about 1.5–3 times for new onset cardiovascular disease in patients with the metabolic syndrome in the absence of diabetes mellitus. In the Framingham Offspring Study

documented it was noted that the population-attributable CVD risk in the metabolic syndrome was 34% among men and only 16% among women. It was an 8-year follow-up of middle aged participants .the same study also found out that metabolic syndrome as well as diabetes are risk factors for ischemic stroke and there is greater risk among patients with the metabolic syndrome than among those with diabetes alone (19% vs. 7%) and a particularly large difference among women (27% vs. 5%).The peripheral vascular disease is also seen in increased incidence in patients with metabolic syndrome.

Type 2 diabetes

There is three to fivefold risk for type 2 diabetes among patients with the metabolic syndrome. The population-attributable risk for developing type 2 diabetes was 62% among men and 47% among women as per Framingham Offspring Study's 8-year follow-up of middle-aged participants.

OTHER ASSOCIATED CONDITIONS

There are many other metabolic alterations that accompany insulin resistance. Apart from the salient features characteristically associated with the metabolic syndrome,the most common alterations include increasein ApoB and ApoCIII, uric acid, prothrombotic factors (fibrinogen,

plasminogen activator inhibitor, asymmetric dimethylarginine, homocysteine, white blood cell count, proinflammatory cytokines, C-reactive protein, microalbuminuria, non-alcoholic fatty liver disease and/or nonalcoholic steatohepatitis, polycystic ovary syndrome, and obstructive sleep apnea.

Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in many parts of the world. NAFLD is strongly associated with overweight/obesity and insulin resistance. But NAFLD can also occur in lean individuals and is particularly common in those with a paucity of adipose depots (i.e., lipodystrophy).The disease includes a spectrum of liver pathology with different clinical prognosis. The simple accumulation of triglyceride within hepatocytes (hepatic steatosis) is the most clinically benign form of disease. On the opposite, most clinically ominous extreme, is cirrhosis and primary liver cancer. In patients with nonalcoholic steatohepatitis, triglyceride accumulation and inflammation coexist. In persons with the metabolic syndrome, approximately 25–60% have nonalcoholic fatty liver disease and around 35% have non-alcoholic steatohepatitis. As the prevalence of overweight/obesity and the metabolic syndrome increases, nonalcoholic steatohepatitis may become one of the

more common causes of end-stage liver disease and hepatocellular carcinoma.

Hyperuricemia

Hyperuricemia reflects defects in insulin action on the renal tubular reabsorption of uric acid and may contribute to hypertension through its effect on the endothelium.

Polycystic ovary syndrome

Polycystic ovary syndrome is highly associated with insulin resistance (50–80%). It is also related with the metabolic syndrome and the prevalence of the syndrome between 40%and 50%. Women with polycystic ovary syndrome are two to four times more likely to have the metabolic syndrome.

Obstructive sleep apnea

Obstructive sleep apnea is commonly associated with obesity, hypertension, increased circulating cytokines, impaired glucose tolerance, and insulin resistance. With these associations, it is not surprising that

individuals with obstructive sleep apnea frequently have the metabolic syndrome. When biomarkers of insulin resistance are compared between patients with obstructive sleep apnea and weight-matched controls, insulin resistance is found to be more severe in those with apnea. Continuous positive airway pressure treatment improves insulin sensitivity in patients with obstructive sleep apnea.

DIAGNOSIS

The diagnosis of the metabolic syndrome relies on fulfilment of the criteria, as assessed using tools at the bedside and in the laboratory. The medical history should include evaluation of symptoms for obstructive sleep apnoea in all patients and polycystic ovary syndrome in premenopausal women. Family history will help to determine risk for CVD and diabetes mellitus. Blood pressure and waist circumference measurements provide information necessary for the diagnosis.

Laboratory Tests Measurement of fasting lipids and glucose is needed in determining whether the metabolic syndrome is present. The measurement of additional biomarkers associated with insulin resistance can be individualized. Such tests might include those for ApoB, high-sensitivity C-reactive protein, fibrinogen, uric acid, urinary microalbumin, and liver function. A sleep study should be performed if symptoms of obstructive sleep apnea are present. If polycystic ovary syndrome is

suspected on the basis of clinical features and anovulation testosterone, luteinizing hormone, and follicle-stimulating hormone should be measured

MANAGEMENT OF METABOLIC SYNDROME

LIFESTYLE MODIFICATION

The weight reduction is the primary approach since obesity is the driving force of this disorder. There occurs improvement in insulin sensitivity when weight is reduced and it results in often favorable modifications in many components of the metabolic syndrome. The recommendations for weight loss include a combination of caloric restriction, increased physical activity and behaviour modification. Caloric restriction is the most important component, whereas increases in physical activity are important for maintenance of weight loss. A high-quality dietary pattern a diet enriched in fruits, vegetables, whole grains, lean poultry, and fish should be encouraged to maximize overall health benefit. Before advising physical activity we should ensure that there is no increased risk due to associated comorbid illness. In patients with sedentary lifestyle, gradual increases in physical activity should be encouraged to enhance adherence and avoid injury. Around 60‑90 min of daily activity is required to achieve the goal of modest weight reduction. If the patient is overweight or obese adult and is unable to undertake activity of 60 to 90 minutes, a significant health benefit will follow from at least 30 min of moderate-intensity activity daily. Behavioural treatment typically includes recommendations for dietary restriction and more physical

activity, resulting in weight loss that benefits metabolic health. The subsequent challenge is the duration of the program because weight regain so often follows successful weight reduction. Long-term outcomes may be enhanced by a variety of methods, such as the internet, social media, and telephone follow-up to maintain contact between providers and patients. In some group of patients, weight reduction measures include medical and surgical therapies. Weight-loss drugs are of two major classes: appetite suppressants and absorption inhibitors. Appetite suppressants approved by the U.S. Food and Drug Administration include phentermine (short duration therapy) as well as the more recent additions phentermine/topiramate and lorcaserin, which are approved without restrictions on the duration of therapy. Metabolic or bariatric surgery is an option for patients with the metabolic syndrome who have a body mass index >40 kg/m2, or >35 kg/m2 with comorbidities. Gastric bypass or vertical sleeve gastrectomy results in dramatic weight reduction and improvement in the features of the metabolic syndrome

TREATMENT OF DYSLIPIDEMIA

A fasting triglyceride value of <150 mg/dL is recommended. In general, the response of fasting triglycerides relates to the amount of weight reduction achieved: a weight reduction of >10% is necessary to lower fasting triglyceride levels. A fibrate (gemfibrozil or fenofibrate) is the drug

of choice to lower fasting triglyceride levels, which are typically reduced by 30‑45%.

In patients with elevated LDL cholesterol studies suggest a linear reduction in CVD events as a result of progressive lowering of LDL cholesterol with statins. For patients with the metabolic syndrome and diabetes, a potent statin (e.g., atorvastatin or rosuvastatin) should be prescribed. The patients with the metabolic syndrome but without diabetes, a score that predicts a 10-year CVD risk exceeding 7.5% should also be treated with statin. Treatment with statins, which lower LDL cholesterol by 15‑60%, is evidence based and is the first-choice medication intervention. Nicotinic acid has modest LDL cholesterol‑lowering capabilities(<20%). Fibrates are best employed to lower LDL cholesterol when both LDL cholesterol and triglycerides are elevated. Very few lipid-modifying compounds increase HDL cholesterol levels. Statins, fibrates, and bile acid sequestrants have modest effects (5‑10%).Nicotinic acid is the only currently available drug with predictable HDL cholesterol-raising properties

TREATMENT OF ELEVATED BLOOD PRESSURE

In patients who have the metabolic syndrome without diabetes, the best choice for the initial antihypertensive medication is an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker,

as these two classes of drugs appear to reduce the incidence of new-onset type 2 diabetes. In all patients with hypertension, a sodium-restricted dietary pattern enriched in fruits and vegetables, whole grains, and low-fat dairy products should be advocated. Home monitoring of blood pressure may assist in maintaining good blood-pressure control.

TREATMENT OF IMPAIRED FASTING GLUCOSE

In patients with the metabolic syndrome and type 2 diabetes, aggressive glycemic control helps in controlling fasting levels of triglycerides and/or HDL cholesterol. In patients with impaired fasting glucose who do not have diabetes, a lifestyle intervention that includes weight reduction, dietary fat restriction, and increased physical activity has been shown to reduce the incidence of type 2 diabetes.

TREATMENT OF INSULIN RESISTANCE

Several drug classes (biguanides, thiazolidinediones [TZDs]) increase insulin sensitivity. Because insulin resistance is the primary pathophysiologic mechanism for the metabolic syndrome, drugs in these classes reduce its prevalence. The mechanism of action of these drugs includes enhancement of insulin action in the liver and suppression of endogenous glucose production. TZDs also improve insulin mediated glucose uptake in muscle and adipose tissue. Benefits of both drugs have

been seen in patients with nonalcoholic fatty liver disease and polycystic ovary syndrome. These drugs also help to reduce the inflammatory markers.

METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE

Many studies have proven that metabolic syndrome increases the premature risk of CVD by around two to three times in the general population.[19]As we know, each of the ingredients of metabolic syndrome exerts an accentuated risk for CVD, so it can be assumed that grouping of components of metabolic syndrome further increases the risk for CVD. It is now accepted that the CVD risk imposed by metabolic syndrome is beyond what is exerted by the components of the syndrome.[20]It was observed in the NHANES observational cohort which was followed up followed for nearly 14 years, metabolic syndrome was a strong predictor of CVD events compared to the individual components. Similar adverse outcomes were also noted in the Finnish study. A large meta analysis has concluded that metabolic syndrome clearly is more dangerous than its components. One thing for sure has emerged that the development of diabetes in subjects with metabolic syndrome confers an added risk for CVD.

RISK FACTORS FOR CARDIO VASCULAR DISEASE

Arterial stiffness is an early signal in the onset and progression of vascular disease in patients with CVD risk factors and for metabolic syndrome. Arterial stiffness is a marker which predicts the risk of future vascular disease. In patients with metabolic syndrome, pulse wave velocity (PWV) is markedly increased reflecting enhanced vascular stiffness.[21,22]Increased PWV (or arterial stiffness) has been observed in patients with hypertension, diabetes, hyperlipidaemia, and obesity. Thus, it is not surprising that subjects with metabolic syndrome have augmented PWV indicating stiffening of the arterial tree, and hence predisposing to premature CVD. Arterial Stiffness results in an increase in pulse wave velocity which can be measured by non invasive methods. On the basis of the pathophysiology of arterial stiffness, it is not surprising that individuals with metabolic syndrome show an increase in the pulse wave velocity. Further research should provide valid information of the utility of pulse wave velocity as a diagnostic or prognostic indicator of metabolic syndrome.

The vascular endothelium is a site and a source of factors maintaining vascular health. The nitric oxide is derived from the endothelium. The action includes vasodilatation andhas anti atherogenic and anti-thrombotic properties. The derangement of the endothelial

dysfunction promotes a state of impaired vascular tone and a prothrombotic milieu in patients with metabolic syndrome.[23,24] Endothelial dysfunction predicts the occurrence of CVD both in the short term as well as the long term. Patients with metabolic syndrome and endothelial dysfunction are at a high risk for the development of CVD.[25] Therefore patients with metabolic syndrome who also demonstrate endothelial dysfunction can be considered as a very high risk category.

It is well known that oxidative stress and vascular inflammation play a role in the pathogenesis of atherosclerosis. Metabolic syndrome appears to be characterized by the presence of proinflammatory markers and oxidative stress.[26] Risk of coronary heart disease is aggravated in patients with metabolic syndrome who have indices of oxidative stress and vascular inflammation. Chronic inflammation and subclinical oxidative stress may occur much before the onset of metabolic syndrome and predispose the patients to premature and accelerated atherosclerosis. Therapeutic probes should be explored to target early signals of vasculopathy in metabolic syndrome so that both the functional and structural complications of the syndrome can be intercepted. High sensitivity C reactive protein (hsCRP) has emerged as a powerful marker of sub clinical as well as clinical atherosclerosis. While a number of inflammatory signals like IL-6 TNF, and cell adhesion molecules have

been identified, hsCRP has been shown to be a sensitive predictor of future cardiovascular events.[27]

Cardiovascular risk factors and markers in metabolic syndrome	
Elevated blood pressure	Arterial stiffness ↑ Pulse wave velocity
Elevated blood glucose	Oxidative Stress
Dyslipidaemia	Vascular inflammation
Obesity	↑ Carotid intima – media thickness

Some observational studies have shown that an increase in the carotid intima media thickness (CIMT) is associated with CVD and CV events standard protocols are widely available for performing CIMT studies properly in the clinical setting. It has been suggested that metabolic syndrome is accompanied by an increase in CIMT. Even in the absence of defined diabetes, metabolic syndrome is associated with increased CIMT. Further studies will shed more light on whether measurement of CIMT adds any value in the evaluation and management of metabolic syndrome. Since endothelial function is deranged at some point in patients with metabolic syndrome, brachial artery flow mediated dilation is altered. Reduced synthesis or availability of nitric oxide is likely responsible for impaired vascular flow reserve in patients with or without metabolic syndrome.

METABOLIC SYNDROME AND CVD INCIDENCE

Several studies have shown that metabolic syndrome is related with an increased cardiovascular risk in females when compared to males. After an 8 year follow up, it was shown that the metabolic syndrome group had a 17.9% incidence as against 4.9% in the non-MS group as shown by Wilson et al [28]. In study conducted in patients without type 2 diabetes, Ingelsson et al (2007) have shown that in MS group, the incidence of CVD was 10.2% and the non-MS group showed an incidence of 4.9%. [29]In another study among Japanese men the CVD prevalence was 12.3% in the MS group compared to 6.5% in the non-MS group[13].In non-obese men with MS, the CVD mortality in the MS group after a follow up of 10 years was found to be 1.99% compared to 0.53% in the non MS group. Also in the general population it was seen that the MS group showed a higher CVD mortality of 7.3% compared to 2.4% in the non MS group as shown by Monami et al (2007). According to the revised NCEP definition for MS, the CVD mortality in the MS group was found to be 7.5% vs 3.9% in the non-MS group.

CONTRIBUTION OF THE INDIVIDUAL RISK FACTORS TO THE GENESIS OF CARDIOVASCULAR RISK

Obesity

Overweight and obesity are increasing in our population. No group is exempt from developing obesity; it occurs in all age groups and both genders. In Indians, subcutaneous fat depots and abdominal obesity predispose to metabolic syndrome and insulin resistance. Abdominal obesity is characterized by increase waist circumference and waist hip ratio. However in Indians, the waist circumference may not be that large but abdominal adiposity is prominent. Enlarged adipocytes are associated with insulin resistance and predispose to diabetes. It is the adipocyte size and distribution which is a factor in the metabolic syndrome among Asian – Indians who actually have BMI values lower that the westerners. By promoting insulin resistance, abdominal adiposity is a significant contributor to CVD risk in patients with metabolic syndrome.

Elevated blood glucose

Diabetes as a risk factor for CVD is well established. Diabetes is an independent risk factor for vascular disease. In conjunction with other CVD risk factors, diabetes aggravates predisposition to various cardiovascular complications. Hence hyperglycemia by itself promotes

atherosclerosis. The major cause of death in patients with diabetes is CVD. By exerting a pro- atherogenic effect, diabetes is also responsible for renal and hypertensive complications in metabolic syndrome. Diabetes causes an increase in carotid intima media thickness. Insulin resistance per se is a risk factor for CVD. Multiple mechanisms may amplify the cardiovascular damage in patients with diabetes. Advanced glycation products, oxidative stress, activation of protein kinaseC, non-enzymatic glycosylation of proteins and lipids and microvascular disease may all play a role in the pathobiology of hyperglycaemia induced vascular disease.

Prothrombotic State

Enhanced thrombosis promotes atherosclerosis and acute cardiovascular events. Endothelial dysfunction is associated with coagulation and fibrinolytic abnormalities.[30] Obesity associated procoagulant state contributes to the risk of acute coronary syndromes. Thrombosis at the site of plaque erosion is a key element in the onset of acute coronary syndromes, furthermore, adipose tissue synthesizes PAI- I which interacts with the coagulation process in causing local thrombosis. High levels of PAI-I and fibrinogen in obesity contribute to the prothrombotic state in metabolic syndrome.

Dyslipidaemia

Dyslipidaemia, a feature of metabolic syndrome is characterized by high triglyceride (TG) low high density lipoprotein cholesterol (HDL- C) levels and free fatty acids. These lipid abnormalities are responsible for atherogenic lipid profile in metabolic syndrome. The dyslipidaemia of metabolic syndrome is also marked by an increase in small TG rich dense LDL particles and Apo B levels. A number of lipid metabolic alterations have been identified in metabolic syndrome; enhanced lipolysis of TG causes an increase in the circulating levels of free fatty acids, peripheral catabolism of TG is also decreased. Additionally hepatic production of lipids is increased. Elevated TG leads to a decrease of HDL particles, thus constituting the classic vasculotoxic lipid trait in metabolic syndrome which is a strong predictor of CV events in metabolic syndrome.

Hypertension

Hypertension is an important feature of metabolic syndrome. Hypertension is a widely prevalent risk factor for CVD. The prevalence of hypertension is on rise across the globe including south Asia. Obesity also contributes to the pathogenesis of hypertension in patients with metabolic syndrome. The endothelial dysfunction and activation of the sympathetic nervous system in metabolic syndrome, results in elevation of the blood pressure levels. An increase in the activity of sympathetic nervous system

(SNS) stimulates the renin angiotensin aldosterone system (RAAS). This causes vasoconstriction and also increased sodium reabsorption from the kidney, thus causing hypertension. The presence of hypertension in metabolic syndrome causes left ventricular hypertrophy and also an increase in CVD mortality. Atherosclerosis reflected by an increase in CIMT is more common in patients with metabolic syndrome who have elevated blood pressure. These findings suggest that hypertension in metabolic syndrome is an important risk factor for CVD and premature mortality.

MECHANISM OF VASCULAR DISEASE IN METABOLIC SYNDROME

The accelerated atherosclerosis plays the pivotal role in the increased cardiovascular disease (CVD) in patients with metabolic syndrome. The proper mechanism is not yet fully understood. Several mechanisms have been postulated. The common components that play a role in increased incidence of cardiovascular disease in metabolic syndrome are

i. Alteration in haemostasis with a prothrombotic state

ii. Endothelial dysfunction

iii. Activity of Adipocytokine

iv. Dyslipidaemia

v. Oxidative stress

vi. Inflammation

I. ALTERED HAEMOSTASIS WITH A PROTHROMBOTIC STATE [31, 32]

The alteration of haemostatic factors has been found to be behind the pathogenesis of vascular disease, in many studies, done in patients with metabolic syndrome. The prothrombotic condition in the blood complicates the pathophysiological process underlying atherosclerotic disease activity. In metabolic syndrome there is simultaneous occurrence of haemostatic alteration and insulin resistance. The plaque develops in the blood vessels over many years, but only cause morbidity when plaque became unstable.

The components that plays role in haemostatic alteration-

1. Plasminogen Activator inhibitor -1 (PAI-1): increased levels of PAI-1 level results in decreased fibrinolysis, which increases atherothrombotic risk.

2. Tissue plasminogen activator (t- PA) : t -PA level is elevated in endothelial dysfunction, leading to instability of the fibrin clot.

3. Factor VIIc : involved in intrinsic coagulation pathway and promotes thrombosis

4. Von Willebrand factor (vWF): The elevated levels of vWF indicate endothelial dysfunction. Increased vWF activity is considered as a marker of subclinical atherosclerosis.

5. Fibrinogen:A marker for ongoing thrombosis.

6. Factor XII: elevated level is seen in association with significant risk factors of cardiovascular disease like elevated triglyceride level, elevated BMI. Its level is strongly correlated with extent of coronary stenosis and previous history of myocardial infarction.

7. Platelets: platelets in persons with insulin resistance are less sensitive to the action of insulin, NO, and PGI2. The activity of platelet is up regulated in setting of insulin resistance.

II. ENDOTHELIAL DYSFUNCTION

The vascular endothelium is a dynamic organ that helps in the maintaining vascular homeostasis. It acts as a physical barrier. The endothelium secretes mediators that regulate vascular tone and interacts with circulatory protein and cells to mediate regulation of platelet functions. Any deterioration of endothelial function promotes vasospasm, thrombosis, vessel occlusion, inflammation and eventually leads to increase in atherosclerosis. Endothelial dysfunction can be assessed by demonstration of impairment of endothelial – depended vasodilatation. Studies have

shown that endothelial dysfunction is seen in healthy subjects with insulin resistance and healthy first degree relatives of patients with Type 2 DM.

III. ADIPOCYTOKINE ACTIVITY

Adipose tissue is recently considered an active endocrine organ. It also helps in storage depots for triglycerides. A large number of adipocyte-derived secretory factors (‘adipokines’) are described in current literature. These points towards the central role of adipose tissue in regulating whole body energy, homeostasis, not only by partitioning lipids into various depots, but also modulating through adipokines. It is well established that individuals who are having obesity and / or metabolic syndrome display a characteristic imbalance of their adipokine profile. This altered adipokine profile results in profound changes in insulin sensitivity. It also affects the metabolism of substrates, making an individual more prone for metabolic disorders. Through their autocrine, paracrine and endocrine functions, adipokines influence a number of organs critical for energy homeostasis.

With the exception of adiponectin and adiposin (complement factor D) most other adipokines show a positive correlation between their circulating levels and adipose tissue mass.

CHIEF ADIPOKINES INVOLVED ARE:

a) Adiponectin – exclusively produced by adipocytes. Adiponectin enhances insulin sensitivity and lipid oxidation. It has a vascular protective effect and also considered to have anti – inflammatory and anti – apoptotic activities. Hypoadiponectinemia has been found in a variety of human metabolic and cardiovascular disease states including type 2 DM, lipodystrophy, non alcoholic hepatic steatosis, essential hypertension and coronary artery disease.

b) Leptin- It is produced form adipose tissue and primarily acts through the hypothalamus. Its levels reflect the index of adipose energy store. Elevated leptin levels reduces desire to eat and helps in energy expenditure. Mutation of the gene producing leptin prevents interaction with the leptin-receptors on the hypothalamus and fails to deliver the satiey signals .This is perceived as starvation leading to further food intake and increase in obesity.

c) Resistin and resistin like molecules (RELM) – it can result in hepatic insulin resistance along with its closely related homologs.

d) Retinol binding protein (RBP4) – RBP4 is found to be involved in insulin resistance. It is produced from both adipose tissue and the liver, and more prominently expressed in visceral fat depots compared to subcutaneous depots. Patients with type 2 diabetes have increased RBP4 levels in plasma along with elevated levels of

transthyretin, a molecule that stabilizes RBP4 and prolongs its half – life.

e) TNF and IL-6 these cytokines are produced from visceral adipocytes and are expressed in excess in patients with metabolic syndrome. TNF increases endothelial endothelin 1 production and decrease fibroblast collagen synthesis. It also stimulates matrix metalloproteinase activity, enchancing the vascular tone and results in increased risk of plaque rupture. IL- 6 induces C – reactive protein production in hepatocytes. All of them are positively correlated with IR.

f) Visfatin – Visfatin is also known as pre–B cell colony–enhancing factor (PBEF). It is also known as nicotinamide phosphoribosyl transferase (NAMPT) since it is the limiting enzyme in nicotinamide adenine dinucleotide (NAD) biosynthesis. Visfatin is expressed in leukocytes, adipocytes, muscle cells and hepatocytes. In adipose tissue, visfatin primarily the product of macrophages which infiltrate to adipocytes. Visfatin may frequently be upregulated in the obese state, its impact on insulin sensitivity and the underlying mechanisms are not clear at this point.

g) Omentin – Omentin is more prominently expressed in omental fat depots. Omentin is found at lower levels patients with glucose intolerance and diabetes.

h) Apelin and vascular endothelial derived growth factor (VEGF)- Apelin plays an important role in the regulation of blood pressure, may have an effect on several immune cells and has pro antigenic properties. As such, it has similar functions as VEGF, another important pro- antigenic factor.

i) Macrophage and monocyte chemoattractant protein-1 (MCP-1)- It has autocrine, paracrine and endocrine function. Acting locally at adipose tissue it decreases insulin stimulated insulin receptor phosphorylation and glucose uptake, thus resulting in insulin resistance. Increased levels of MCP–1 in circulation increases the number and adhesion potential of circulating monocytes to injured arterial wall, thus enhances neo-intimal formation.

IV. DYSLIPIDAEMIA

Insulin is an anabolic hormone has immense effect on fat metabolism. It inhibits adipocyte lipolysis by promoting non-esterified fatty acid (NEFA) re-esterification.An increase in plasma insulin level can cause sharp fall in NEFA level. In metabolic syndrome, NEFA level

increases leading to increased lipolysis, increased release of adipocytokines, diminished glucose uptake, hypertriglyceridemia, low high density lipoprotein (HDL) and increased oxidised low density lipoproteins (LDL). Oxidation, which is enhanced in metabolic syndrome, modifies the phospholipid content of LDL and the amino acid side chains of Apo protein B 100 (Apo B 100). The oxidised Apo B 100 results in excess of receptor uptake of LDL by endothelial cells. Oxidised LDL increases the adhesion of circulating monocytes to damaged endothelium whereby it enhances their migration into the vascular intima. Oxidised LDL when compared with LDL is more immunogenic. It produces antibody-lipoprotein complex which stimulate foam cell formation and platelet aggregation as compared to nonoxidised LDL.This triad of Hypertriglyceridemia, low HDL and increased LDL levels happen in patients with insulin resistence and is termed as atherogenic lipoprotein phenotype.

V. OXIDATIVE STRESS

The common pathophysiology associated with endothelial dysfunction are abnormal production of reactive oxygen species (ROS) and the subsequent decrease in vascular bioavailability of nitric oxide (NO).This occurs in association with hypercholesterolemia, diabetes mellitus, chronic smoking, metabolic syndrome and hypertension.

Superoxide produced by the nicotinamide dinucleotide phosphate (NADP) oxidase, mitochondrial sources, or the xanthine oxidase may react with NO thereby resulting in excessive formation of peroxynitrite, a reactive nitrogen species that has been demonstrated to accelerate the atherosclerotic process by causing direct structural damage and by causing further ROS production.

The beta cells are low in free – radical quenching enzyme such as catalase glutathione peroxidise and superoxide dismutase. This results in increased vulnerability of the β cells in the islets of Langerhans. The cells are also damaged by prolonged hyperglycaemia, increased free fatty acid (FFA) and ROS levels. This results in deterioration of beta cell function

The antioxidants such as Vitamin E, vitamin C, glutathione are shown to improve insulin sensitivity in several studies. The substances such as stains, angiotensin converting enzyme inhibitors or angiotensin1 receptor blockers possess indirect antioxidant properties mediated by the stimulation of NO production and simultaneous inhibition of superoxide production. Hence oxidative stress remains an attractive target for cardiovascular prevention and therapy.

VI. INFLAMMATION [33,34]

Studies and current evidences have shown that inflammation plays more important role in the process of initiation, progression and complication of atherosclerosis.

As cardiovascular diseases (CVD) can precede the development of Type 2 DM, the notion that both conditions share some common genetic and environmental antecedents, has been put forward (The 'common soil hypothesis') raising the possibility that inflammation could be the bridging ling between MS and atherosclerosis. Recent studies have been confirming the positive association between obesity indices and inflammatory markers, mainly C – reactive protein, Fibrinogen, PAI -1. CRP elicits direct pro atherogenic and pro inflammatory effect to act as a direct mediator of endothelial dysfunction.

Metabolic syndrome in South Asians

The prevalence of MS in the South Asian population in increasing. There are many potential risk factors associated with the development of MS in the South Asian population some of which are as follows

1. Urbanization
2. Less physical activity
3. High carbohydrate, high fat and low fiber food

4. Low intake of w-3 PUFAs
5. Increasing life expectancy of the elderly population
6. Migration from villages to cities
7. Stress
8. Alcohol and tobacco consumption

The major disadvantage in the assessment of metabolic syndrome in South Asians is the scarcity of nationally representative data from any country. A study form south India has estimated the prevalence of MS to be 25.8% by the IDF criteria, 23.2% by the WHO criteria and 18.3% by the NCEP ATP III criteria. Moreover the conventional risk factors comprising the metabolic syndrome are highly prevalent in the Asian Indians. It has been shown that the prevalence of risk factors is as follows abdominal obesity 31.4%, hypertension 55.4%; low HDL 65.5% and raised fasting glucose 26.7%. The high prevalence of MS in Indians could be because of the higher prevalence of insulin resistance. Even in younger populations the prevalence of insulin resistance has been shown to be four fold higher than that of other ethnic groups. Moreover, Indians show very low levels of HDL compared to other populations which could increase their risk of metabolic syndrome. The levels of LDL and atherogenic small dense LDL have also been reported to be higher among the South Asians.

MATERIALS AND METHODS

Patients aged < 45 years hospitalized with the first episode of ACS were categorized based on the MODIFIED NCEP-ATP III CRITERIA for metabolic syndrome.

ATP III identified 6 components of the metabolic syndrome that relate to CVD:

● Abdominal obesity

● Atherogenic dyslipidemia

● Raised blood pressure

● Insulin resistance / glucose intolerance

● Proinflammatory state

● Prothrombotic state

NATIONAL CHOLESTEROL EDUCATION PROGRAM AND ADULT TREATMENT PANEL III. (NCEP:ATPIII)

Three or more of the following:

• Central obesity: waist circumference >102 cm (M), >88 cm (F)

• Hypertriglyceridemia: triglyceride level ≥150 mg/dL or specific medication

• Low HDLc cholesterol: <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication

• Hypertension: blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic or specific medication

• Fasting plasma glucose level ≥100 mg/dL or specific medication or previously diagnosed type 2 diabetes

Laboratory assessments included obtaining venous blood samples in a fasted state for the determination of lipid components (total cholesterol (TC), HDL-C, LDL-C and TG, and total lipid) and blood glucose. Serum glucose and lipids were measured by International Federation of Clinical Chemistry (IFCC) approved enzymatic methods using commercially available kits. Blood pressure was measured using a sphygmomanometer and elevated blood pressure according to NCEP:ATPIII was diagnosed if the systolic blood pressure (SBP) was higher than 130mmHg or the diastolic bloodpressure (DBP) was above 85 mmHg. Waist circumference (WC) was evaluated at midway between the iliac crest and the last rib.

STUDY AREA

ICCU/IMCU/CARDIOLOGY, MEDICINE WARDS OF TVMCH

STUDY PERIOD

AUGUST 2016 – AUG 2017

INCLUSION CRITERIA

Patients aged < 45 years hospitalized with the first episode of ACS

EXCLUSION CRITERIA

Patients of age more than 45years

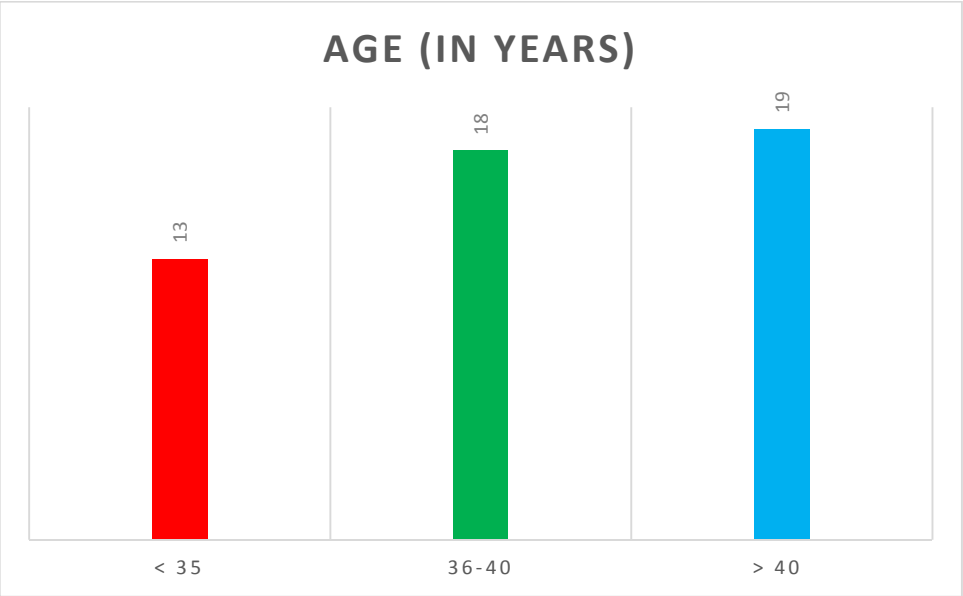
Type 1 diabetes patients

Patients with metabolic disorders

OBSERVATIONS AND RESULTS

AGE DISTRIBUTION

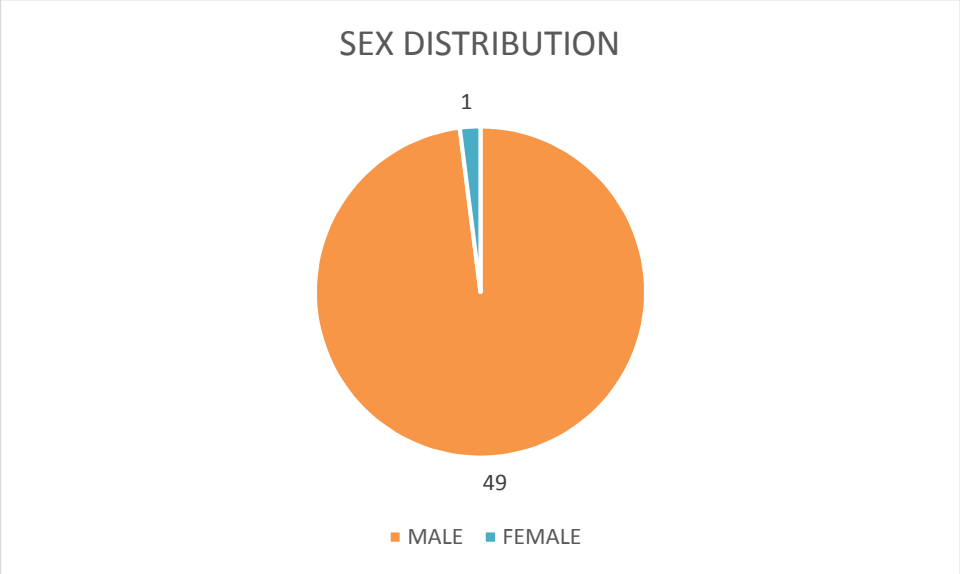
AGE (IN YEARS)	NO OF PATIENTS	PERCENTAGE
< 35	13	26%
36-40	18	36%
> 40	19	38%



Among the sample population, 13 patients (26%) were below the age of 35, 18 pateints (36%)were having age between 36 and 40. There were 19 patients (38%)above 40 years of age.

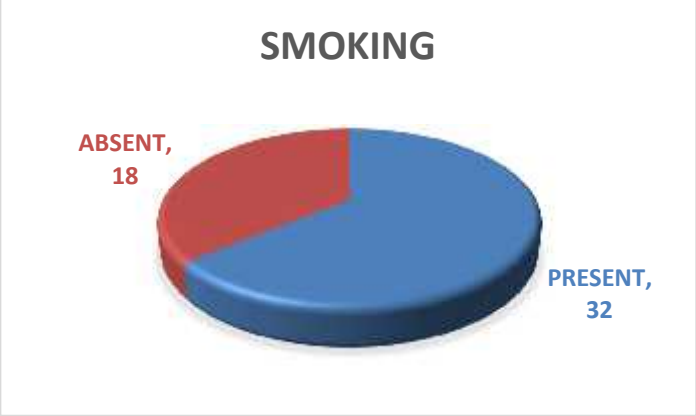
SEX DISTRIBUTION

SEX	NO OF PATIENTS	PERCENTAGE
MALE	49	98%
FEMALE	1	2%



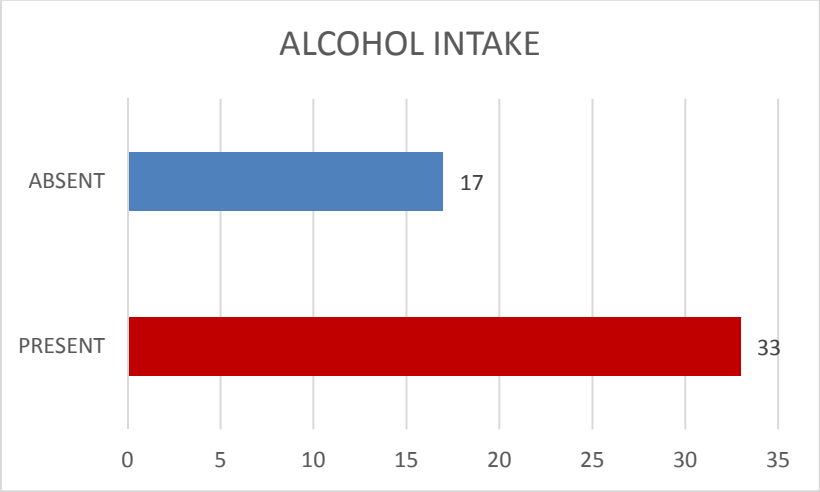
Most of the patients in sample population were males (98%). There was only one single female patient.

SMOKING	NO OF PATIENTS	PERCENTAGE
PRESENT	32	64%
ABSENT	18	36%



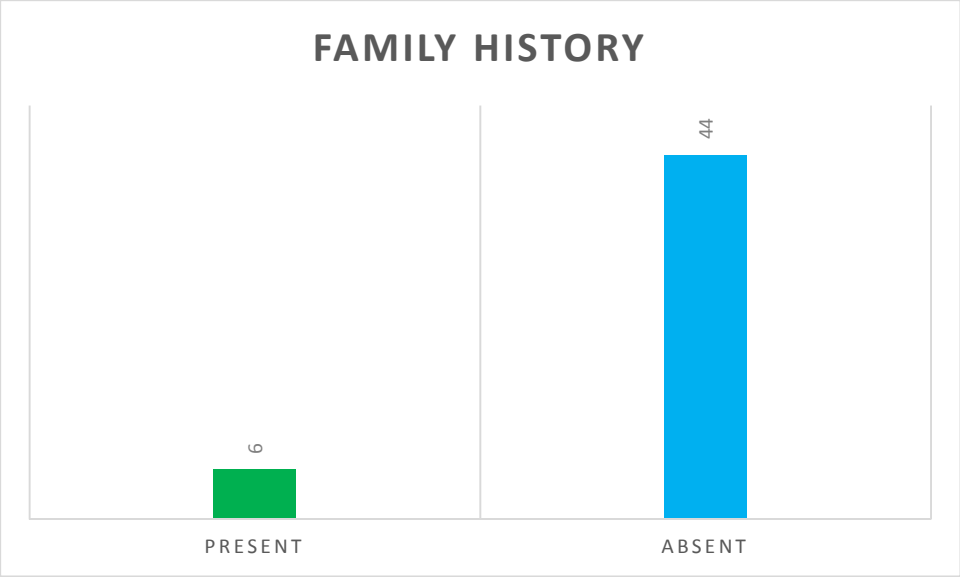
Among the sample population smoking was present in 32 patients (64%) and the remaining 18 patients (36%) were non smokers.

ALCOHOL INTAKE	NO OF PATIENTS	PERCENTAGE
PRESENT	33	66%
ABSENT	17	34%



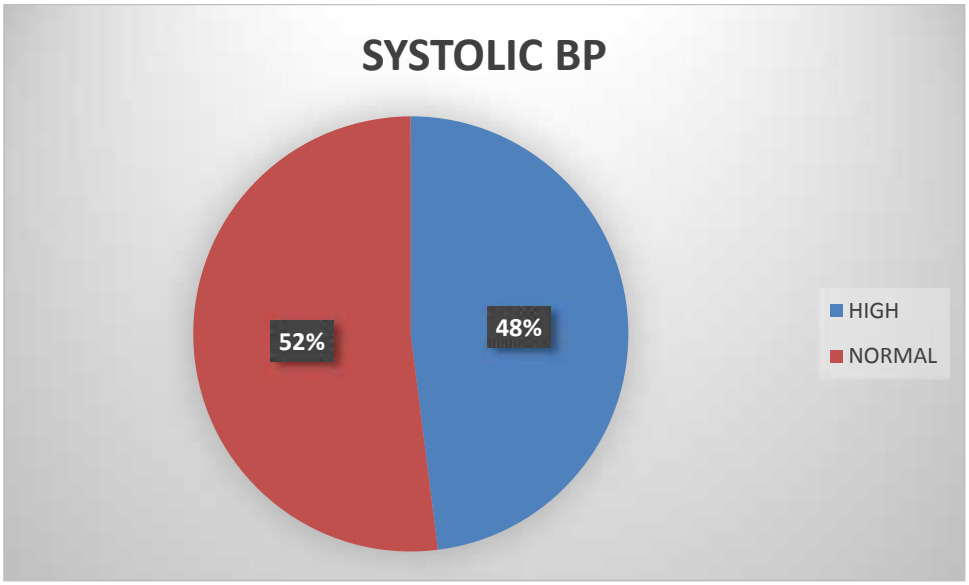
Among the sample population alcohol consumption was present in 33 patients (66%) and the remaining 17 patients (34%) did not consume alcohol.

FAMILY HISTORY	NO OF PATIENTS	PERCENTAGE
PRESENT	6	12%
ABSENT	44	88%



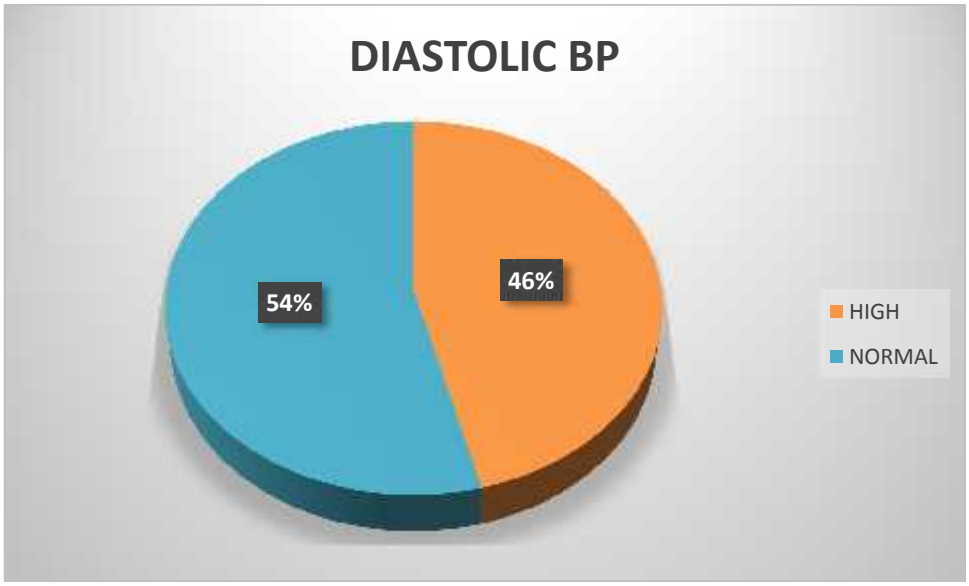
The family history suggestive of metabolic syndrome was present in 6 patients (12%). Family history of metabolic syndrome was not present in 44 patients (88%) .

SYSTOLIC BP	NO OF PATIENTS	PERCENTAGE
HIGH	24	48%
NORMAL	26	52%



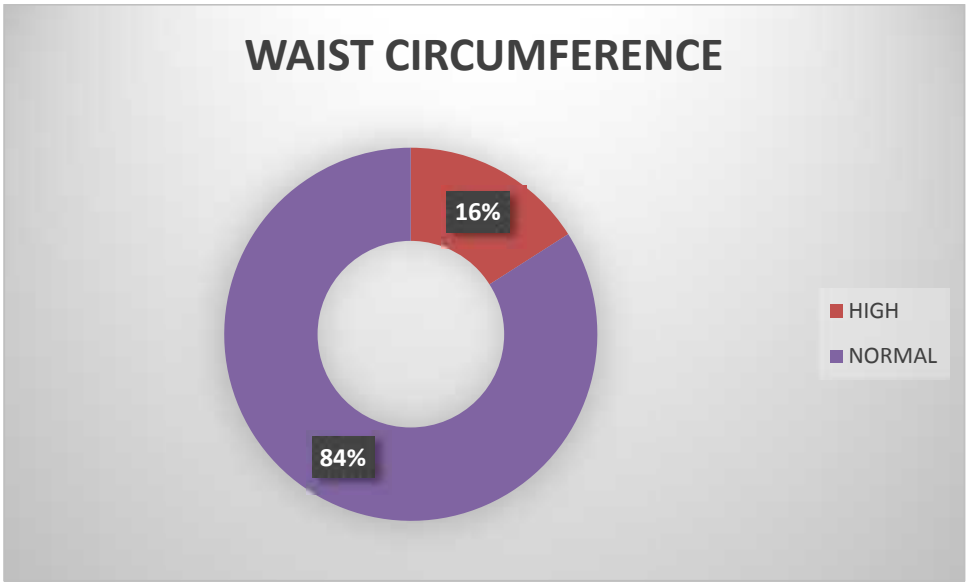
Elevated systolic blood pressure was noted in 24 patients (48%) among the study population

DIASTOLIC BP	NO OF PATIENTS	PERCENTAGE
HIGH	23	46%
NORMAL	27	54%



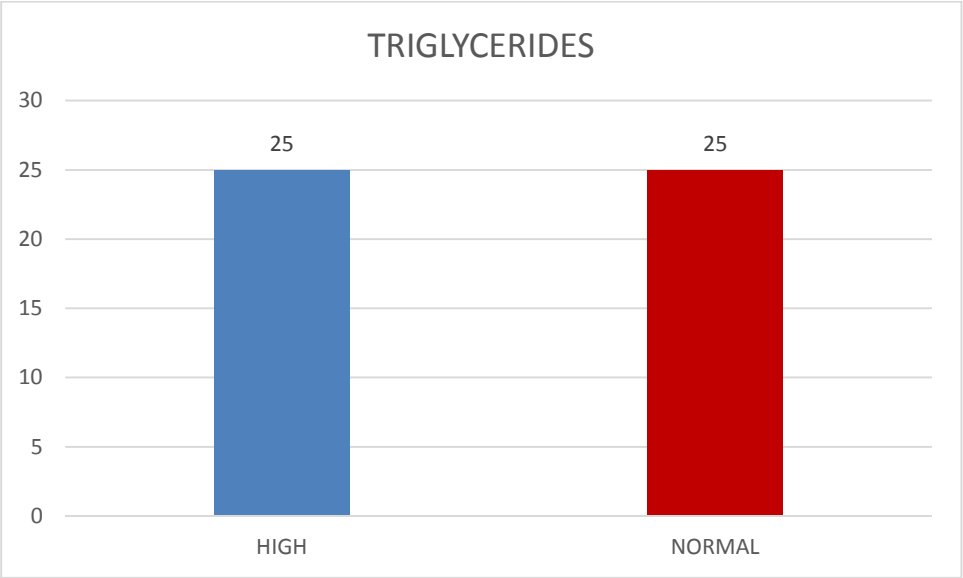
Elevated diastolic blood pressure was noted in 23 patients (46%) among the study population.

WAIST CIRCUMFERNCE	NO OF PATIENTS	PERCENTAGE
HIGH	8	16%
NORMAL	42	84%



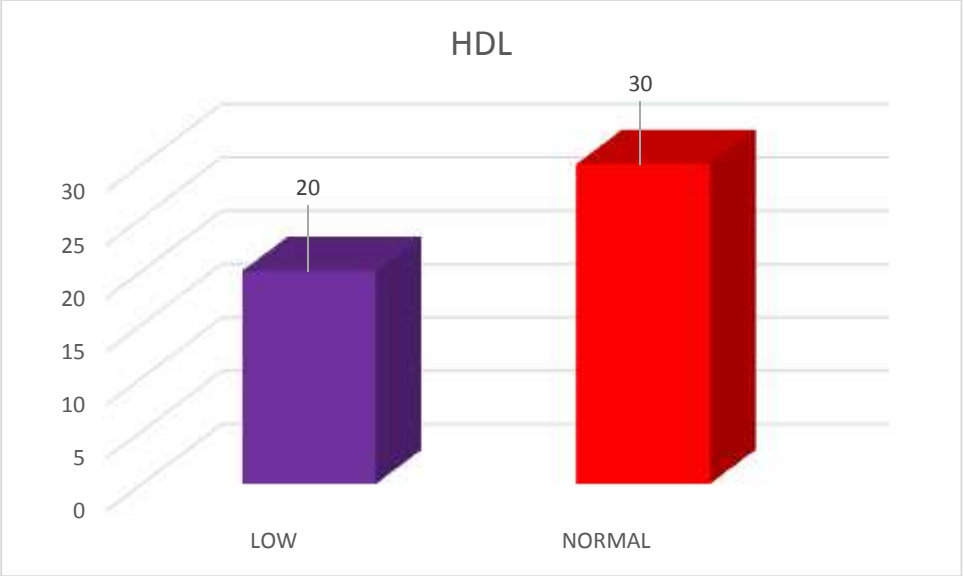
Among the study population 8 patients (16%) had increased waist circumference and 42 patients (84%) had normal waist circumference.

TRIGLYCERIDES	NO OF PATIENTS	PERCENTAGE
HIGH	25	50%
NORMAL	25	50%



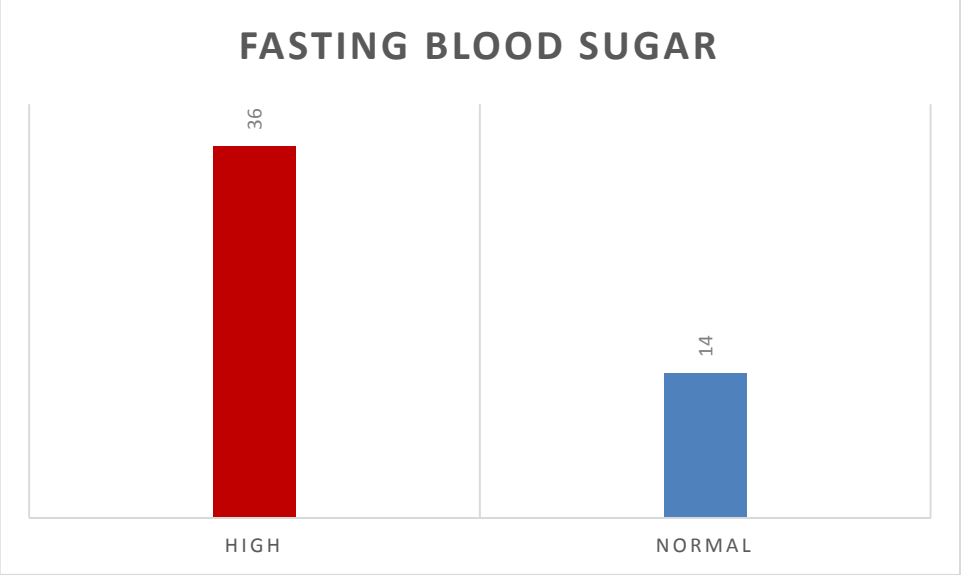
Triglycerides was found to be high in 25 patients (50%) among sample population and 25 patients (50%) had normal levels.

HDL	NO OF PATIENTS	PERCENTAGE
LOW	20	40%
NORMAL	30	60%



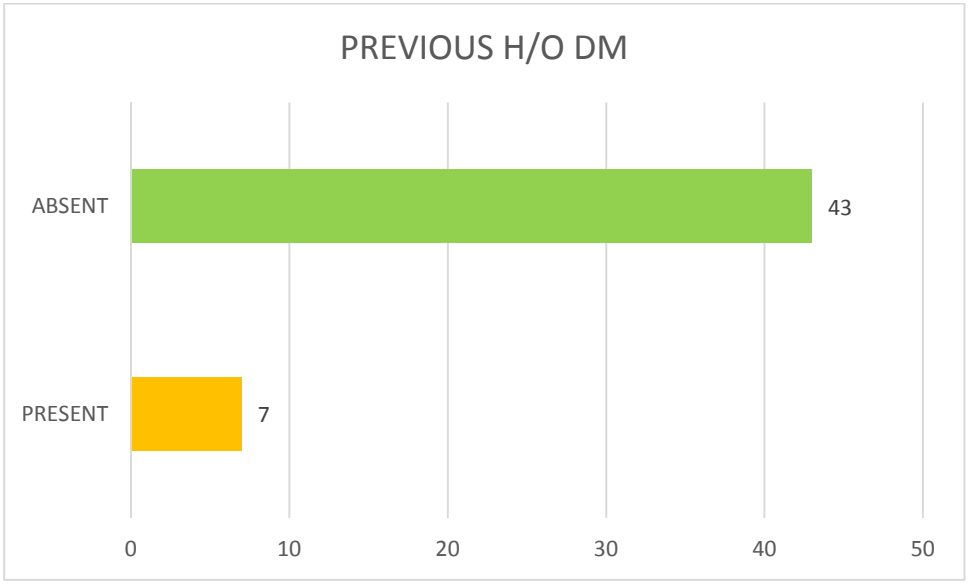
Serum HDL was found to be low in 20 patients (40%) among sample population and 30 patients (60%) had normal levels.

FBS	NO OF PATIENTS	PERCENTAGE
HIGH	36	72%
NORMAL	14	28%



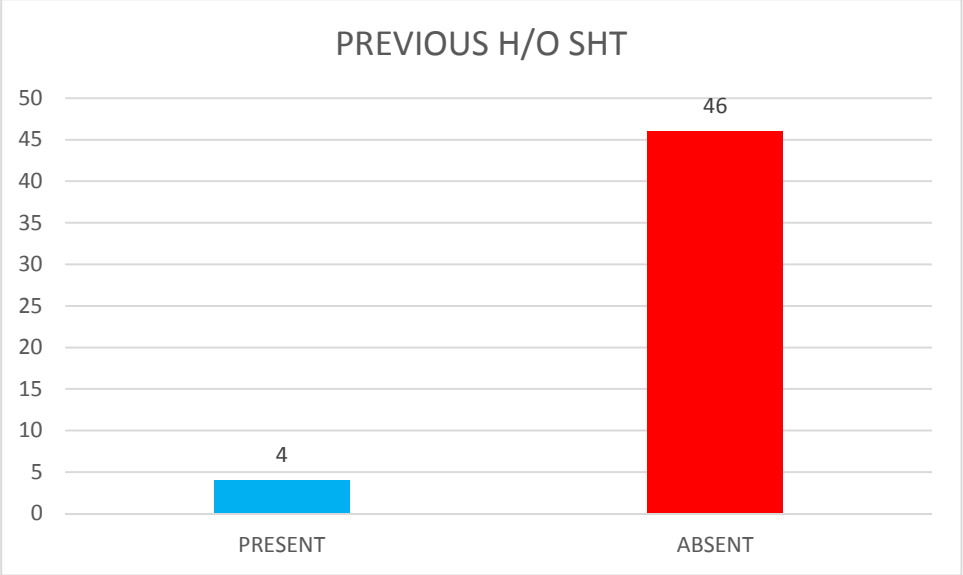
Fasting blood sugar was high in 36 patients (72%) among sample population and 14 patients (28%) had normal levels.

PREVIOUS H/O DM	NO OF PATIENTS	PERCENTAGE
PRESENT	7	14%
ABSENT	43	86%



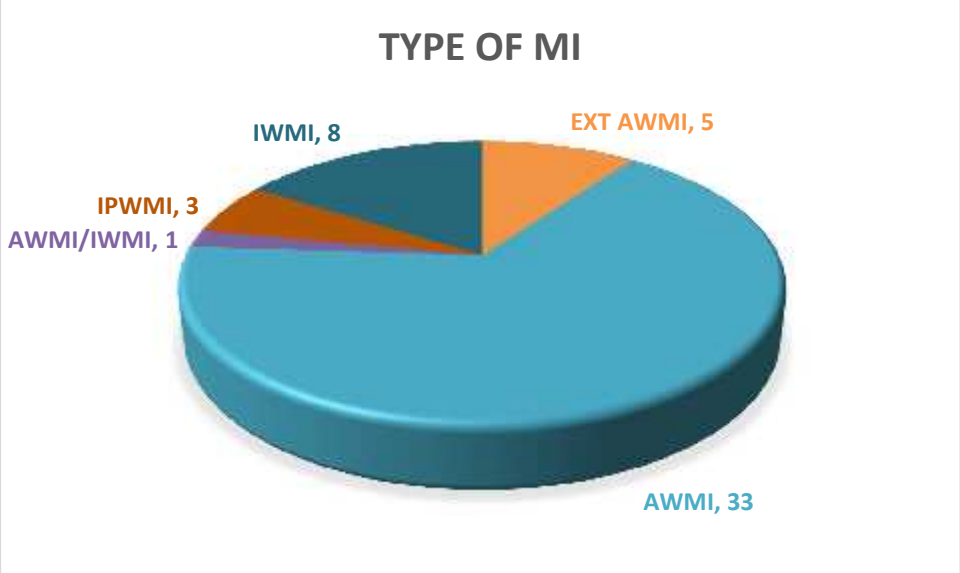
The history of diabetes mellitus was present in 7 patients (14%). Family history of diabetes mellitus was absent in 43 patients (86%)

PREVIOUS H/O SHT	NO OF PATIENTS	PERCENTAGE
PRESENT	4	8%
ABSENT	46	92%



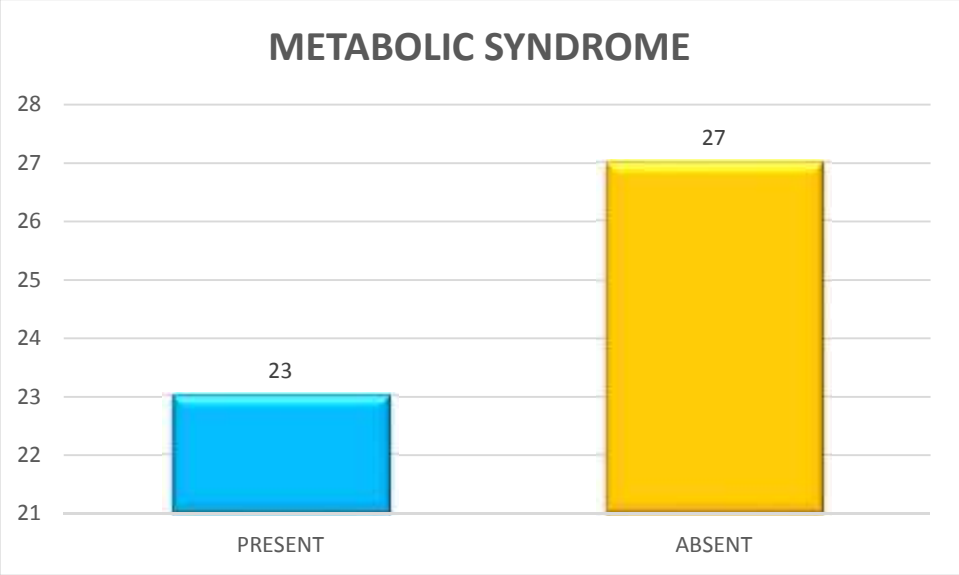
Among the study population, the history of systemic hypertension was present in 4 patients (8%). Family history of systemic hypertension was absent in 46 patients (92%)

TYPE OF MI	NO OF PATIENTS	PERCENTAGE
EXTENSIVE AWMI	5	10%
AWMI	33	66%
AWMI/IWMI	1	2%
IPWMI	3	6%
IWMI	8	16%



Among the study population admitted with acute coronary syndromes, the types of MI were as follows. The most common was AWMI which was seen in 33 patients (66%). Extensive anterior wall MI in 5 patients (10%), AWMI/IWMI in 1 patient (2%), IWMI in 8 patients (16%), IPWMI in 3 patients (6%).

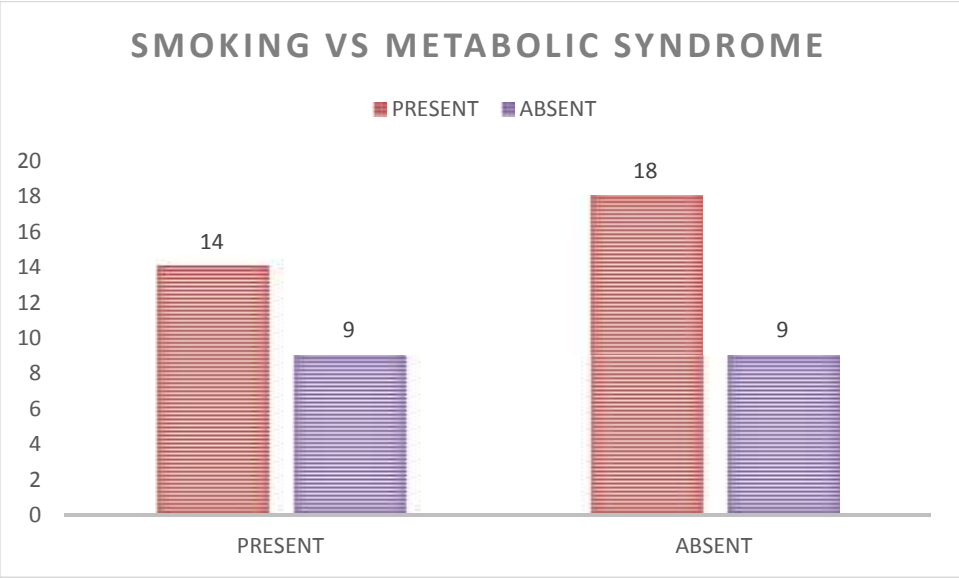
METABOLIC SYNDROME	NO OF PATIENTS	PERCENTAGE
PRESENT	23	46%
ABSENT	27	54%



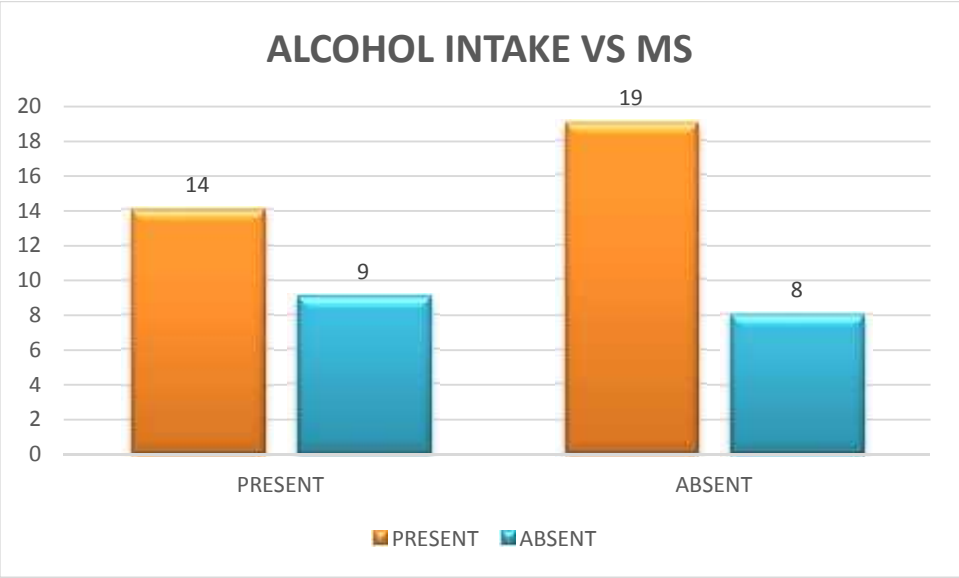
Among the study population metabolic syndrome was present in 23patients (46%). The metabolic syndrome was not present in 27 patients (54%) in this study.

DEMOGRAPHIC FEATURES		
PARAMETER	**MEAN**	**SD**
AGE	38.48	4.95
SBP	126.2	18.61
DBP	84.8	15.15
WC	89.2	9.13
TGL	173.02	77.83
HDL	40.44	5.41
FBS	130.9	54.2

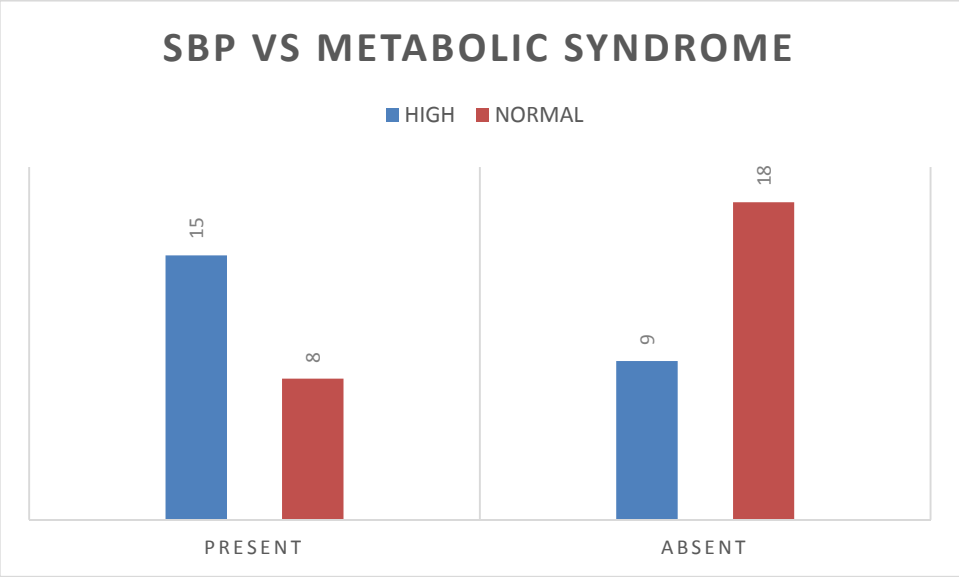
	METABOLIC SYNDROME	
SMOKING	**PRESENT**	**ABSENT**
PRESENT	14	18
ABSENT	9	9
P VALUE - 0.670		
NON SIGNIFICANT		
ODDS RATIO - 0.758		
CHI SQUARE TEST		



	METABOLIC SYNDROME	
ALCOHOL INTAKE	**PRESENT**	**ABSENT**
PRESENT	14	19
ABSENT	9	8
P VALUE - 0.480		
NON SIGNIFICANT		
ODDS RATIO - 0.655		
CHI SQUARE TEST		

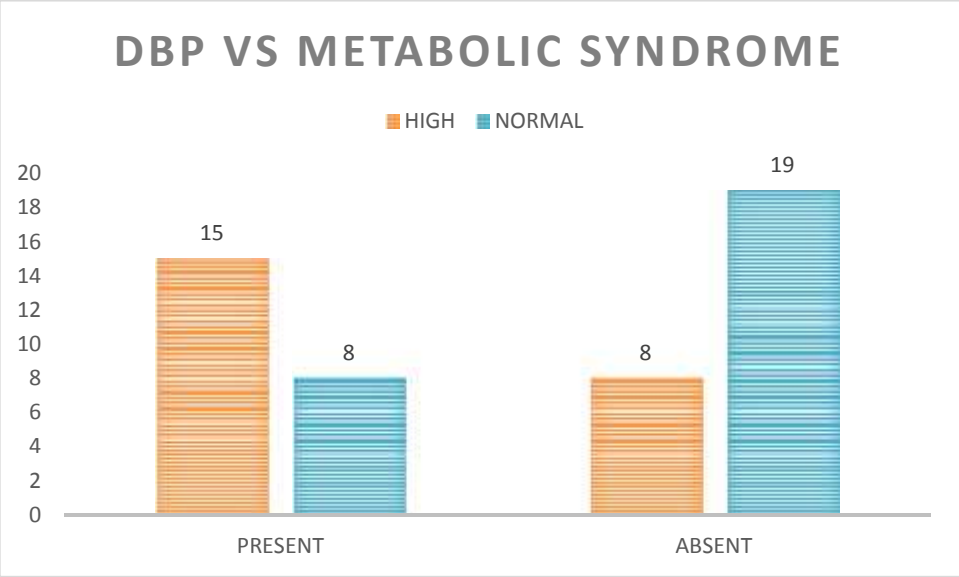


	METABOLIC SYNDROME	
SYSTOLIC BP	**PRESENT**	**ABSENT**
HIGH	15	9
NORMAL	8	18
P VALUE - 0.025		
SIGNIFICANT		
ODDS RATIO - 3.75		
CHI SQUARE TEST		



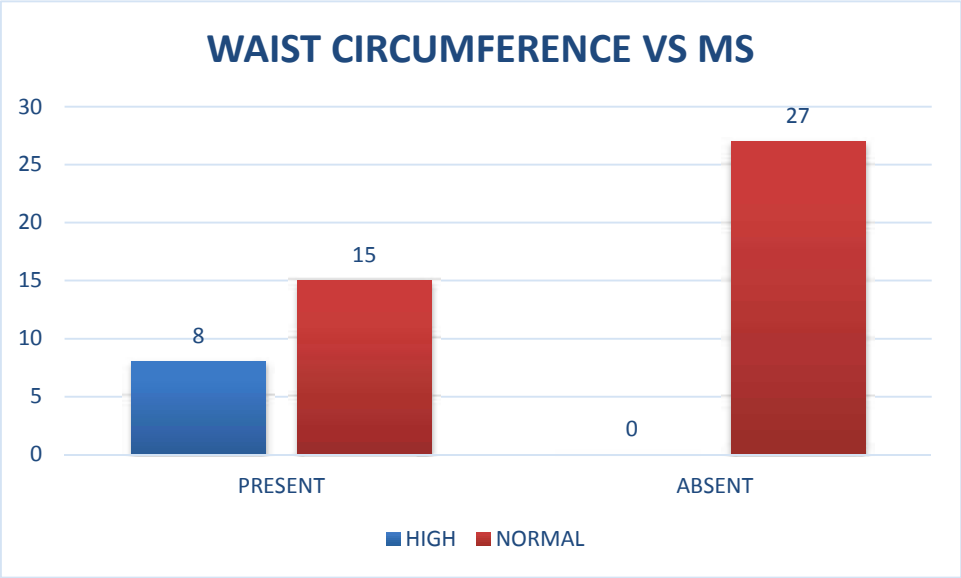
Statistically significant correlation was found between elevated systolic blood pressure and metabolic syndrome.

	METABOLIC SYNDROME	
DIASTOLIC BP	**PRESENT**	**ABSENT**
HIGH	15	8
NORMAL	8	19
P VALUE - 0.012		
SIGNIFICANT		
ODDS RATIO - 4.45		
CHI SQUARE TEST		



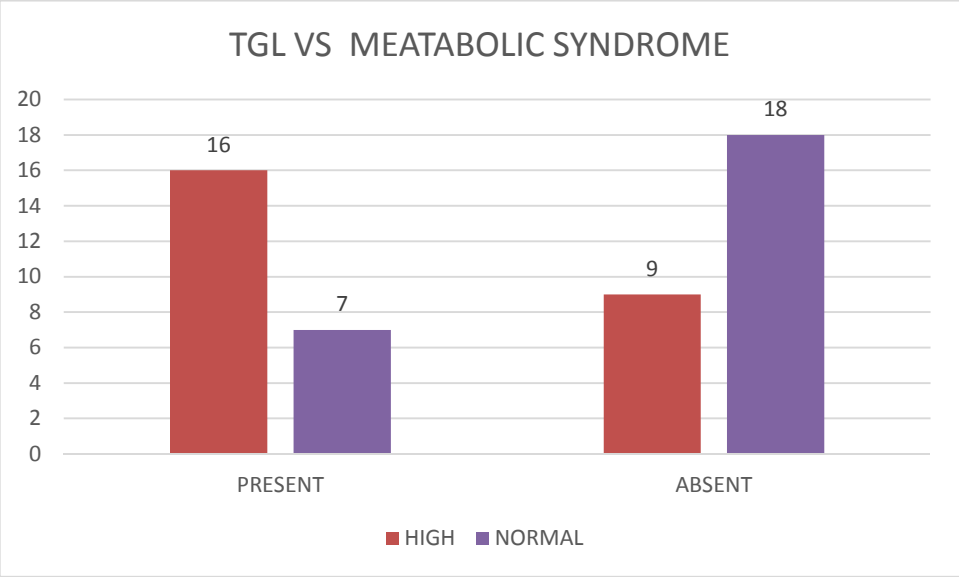
Statistically significant correlation was found between elevated diastolic blood pressure and metabolic syndrome.

	METABOLIC SYNDROME	
WAIST CIRCUMFERENCE	**PRESENT**	**ABSENT**
HIGH	8	0
NORMAL	15	27
P VALUE - 0.001		
SIGNIFICANT		
ODDS RATIO - 2.8		
CHI SQUARE TEST		



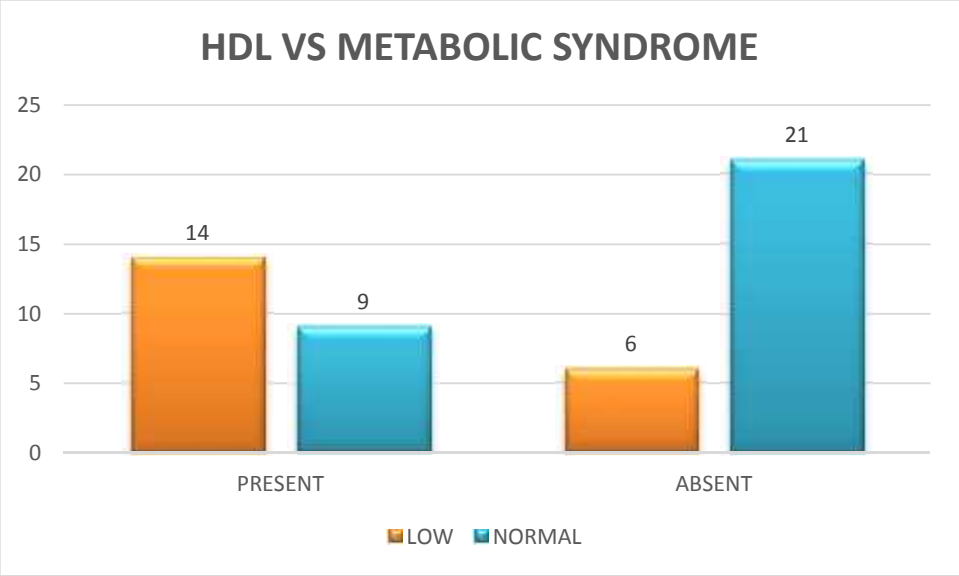
Statistically significant correlation was found between increased waist circumference and metabolic syndrome

	METABOLIC SYNDROME	
TRIGLYCERIDES	**PRESENT**	**ABSENT**
HIGH	16	9
NORMAL	7	18
P VALUE - 0.011		
SIGNIFICANT		
ODDS RATIO - 4.57		
CHI SQUARE TEST		



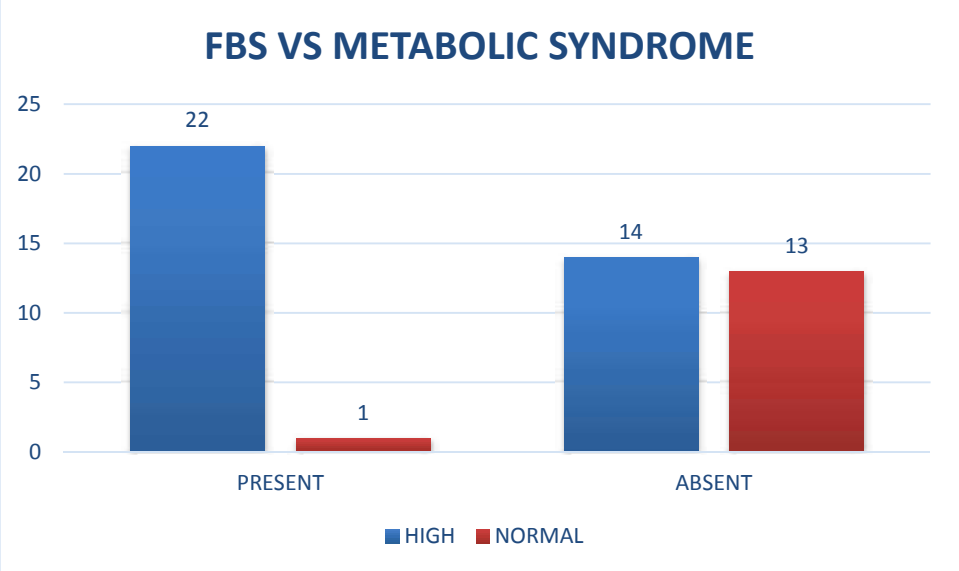
Statistically significant correlation was found between elevated triglycerides levels and metabolic syndrome.

	METABOLIC SYNDROME	
HDL	**PRESENT**	**ABSENT**
LOW	14	6
NORMAL	9	21
P VALUE - 0.005		
SIGNIFICANT		
ODDS RATIO - 5.44		
CHI SQUARE TEST		



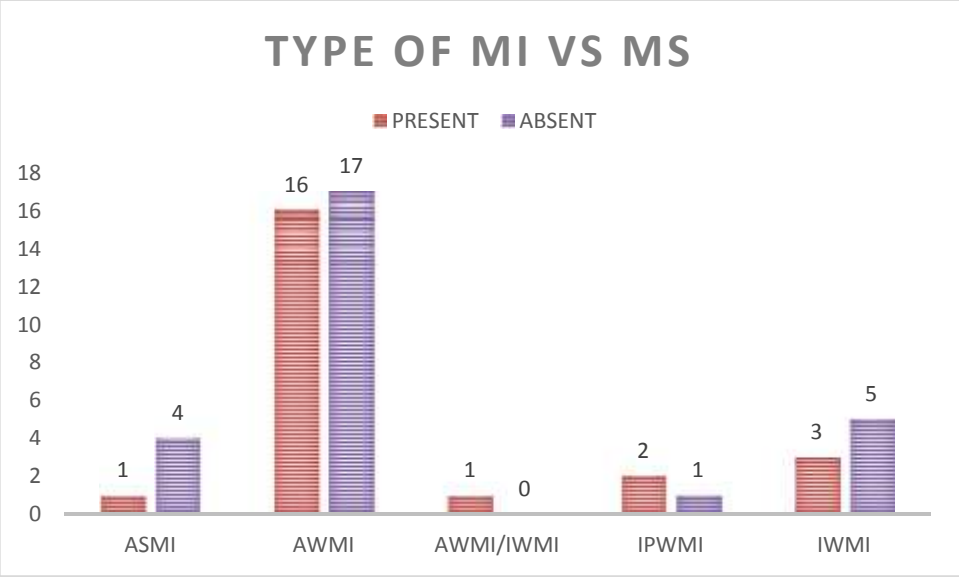
Statistically significant correlation was found between lower HDL cholesterol levels and metabolic syndrome.

	METABOLIC SYNDROME	
FASTING BLOOD SUGAR	**PRESENT**	**ABSENT**
HIGH	22	14
NORMAL	1	13
P VALUE - 0.001		
SIGNIFICANT		
ODDS RATIO - 20.42		
CHI SQUARE TEST		



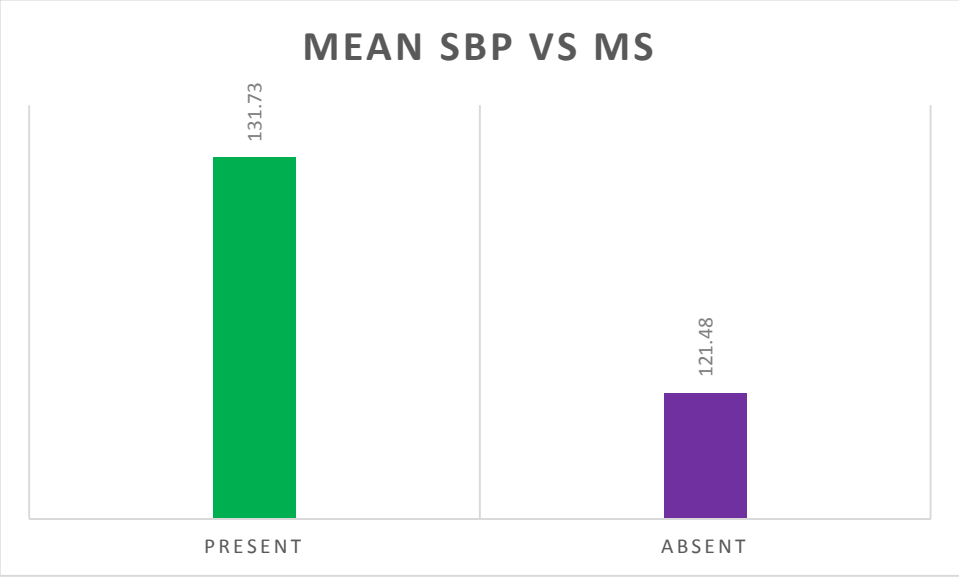
Among the 23 patients with metabolic syndrome, 22 patients had elevated fasting blood glucose levels and one had normal levels. Statistically significant correlation was found between elevated fasting blood glucose levels and metabolic syndrome.

	METABOLIC SYNDROME	
TYPE OF MI	**PRESENT**	**ABSENT**
EXT AWMI	1	4
AWMI	16	17
AWMI/IWMI	1	0
IPWMI	2	1
IWMI	3	5
P VALUE - 0.499		
NON SIGNIFICANT		
KRUSKAL WALLIS TEST		



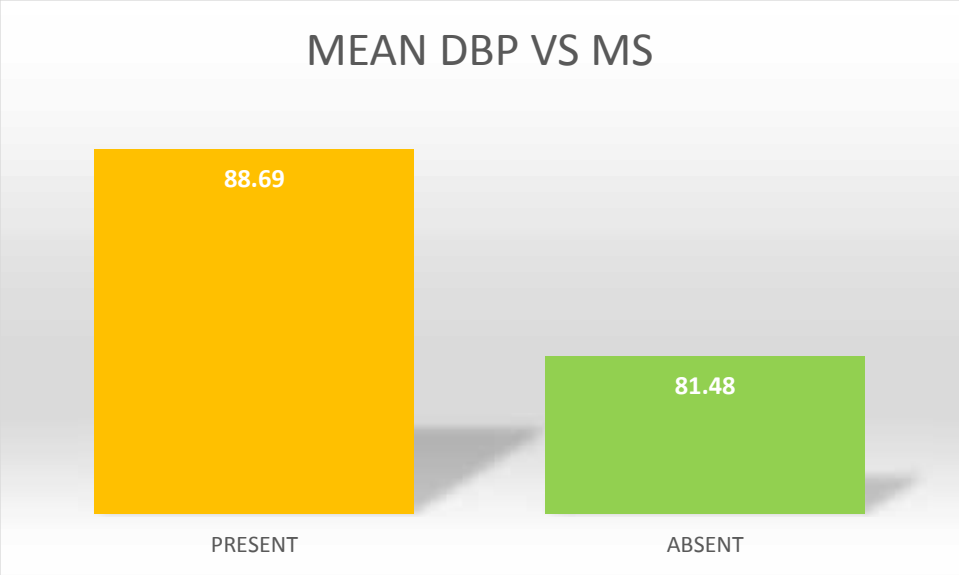
No significant correlation was found between the type of MI and metabolic syndrome.

	SYSTOLIC BLOOD PRESSURE	
METABOLIC SYNDROME	**MEAN**	**SD**
PRESENT	131.73	16.41
ABSENT	121.48	19.35
P VALUE - 0.05		
SIGNIFICANT		
UNPAIRED T TEST		



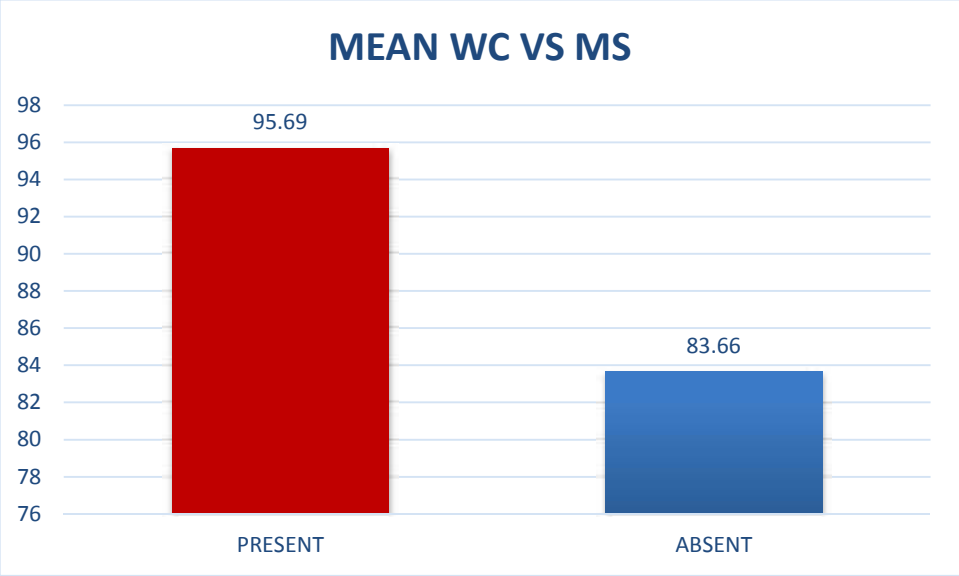
The mean systolic blood pressure was found to be 131.73 mmhg in patients with metabolic syndrome and 121.48mmhg in patients without metabolic syndrome.

	DIASTOLIC BLOOD PRESSURE	
METABOLIC SYNDROME	**MEAN**	**SD**
PRESENT	88.69	12.54
ABSENT	81.48	16.57
P VALUE - 0.094		
NON SIGNIFICANT		
UNPAIRED T TEST		



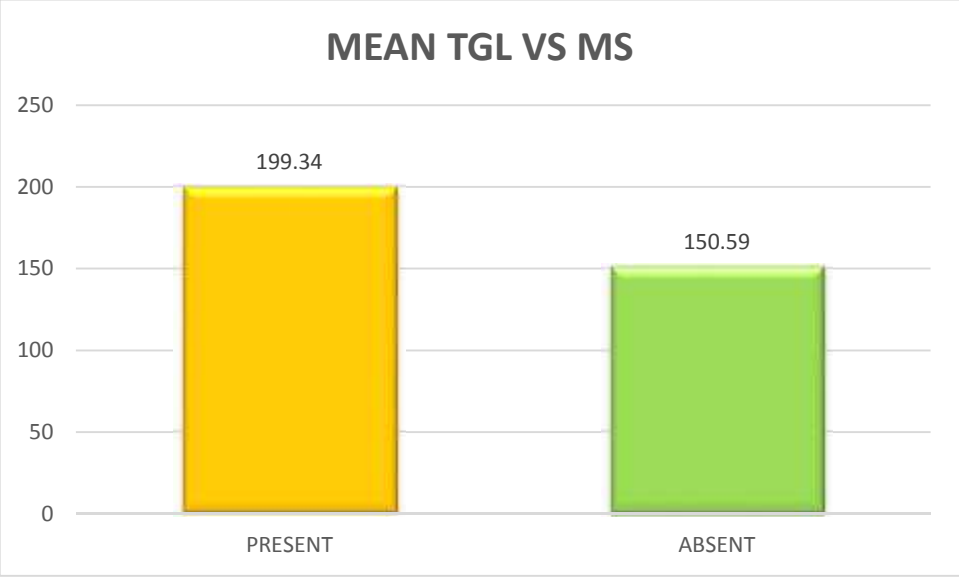
The mean diastolic blood pressure was found to be 88.69mmhg in patients with metabolic syndrome and 81.48mmhg in patients without metabolic syndrome. The difference was found to be statistically significant.

	WAIST CIRCUMFERENCE	
METABOLIC SYNDROME	**MEAN**	**SD**
PRESENT	95.69	7.05
ABSENT	83.66	6.78
P VALUE - 0.001		
SIGNIFICANT		
UNPAIRED T TEST		



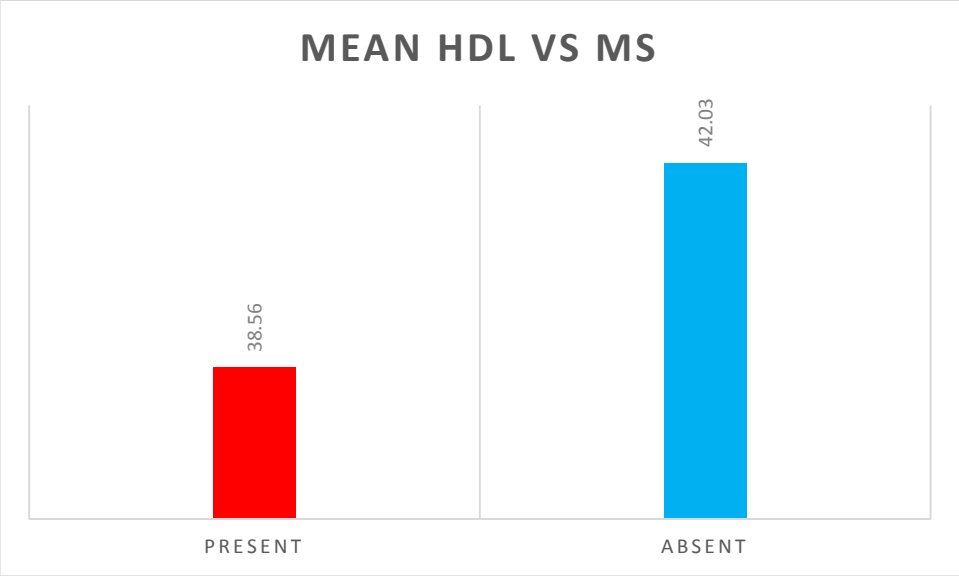
The mean waist circumference was found to be 95.69cm in patients with metabolic syndrome and 83.66cm in patients without metabolic syndrome. The difference was found to be statistically significant.

	TRIGLYCERIDE	
METABOLIC SYNDROME	**MEAN**	**SD**
PRESENT	199.34	90.79
ABSENT	150.59	57.48
P VALUE - 0.026		
SIGNIFICANT		
UNPAIRED T TEST		



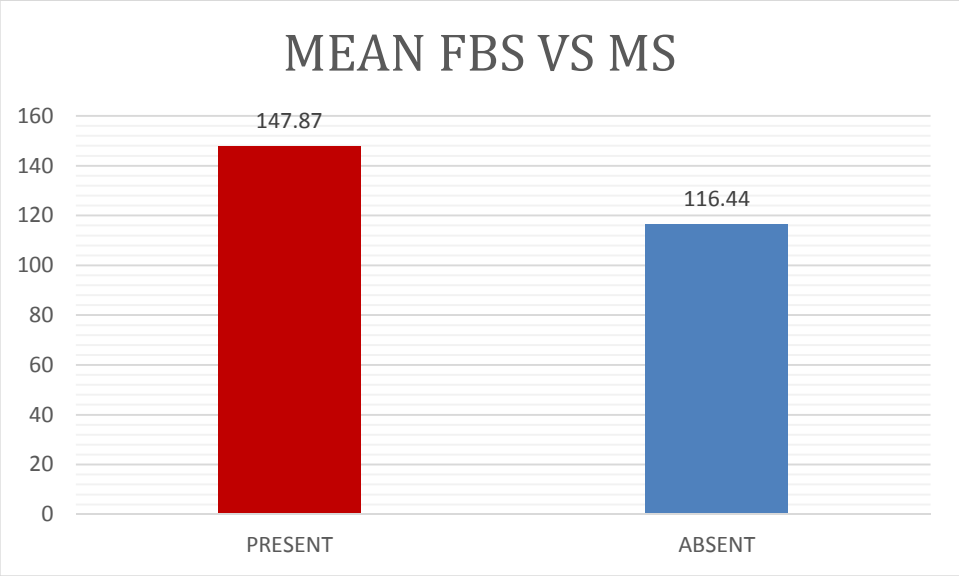
The mean triglyceride level was found to be 199.34 mg/dl in patients with metabolic syndrome and 150.59mg/dl in patients without metabolic syndrome. The difference was found to be statistically significant.

	HIGH DENSITY LIPOPROTEIN	
METABOLIC SYNDROME	**MEAN**	**SD**
PRESENT	38.56	6.3
ABSENT	42.03	3.87
P VALUE - 0.022		
SIGNIFICANT		
UNPAIRED T TEST		



The mean high density lipoprotein cholesterol level was found to be 38.56 mg/dl in patients with metabolic syndrome and 42.03 mg/dl in patients without metabolic syndrome. The difference was found to be statistically significant

	FASTING BLOOD SUGAR	
METABOLIC SYNDROME	**MEAN**	**SD**
PRESENT	147.87	67.32
ABSENT	116.44	34.54
P VALUE - 0.039		
SIGNIFICANT		
UNPAIRED T TEST		



The mean fasting blood sugar level was found to be 147.87mg/dl in patients with metabolic syndrome and 116.44 mg/dl in patients without metabolic syndrome. The difference was found to be statistically significant

PEARSON CORRELATION			
PARAMETER	**R VALUE**	**P VALUE**	**SIGNIFICANT**
AGE	0.098	0.496	NO
SYSTOLIC BP	0.277	0.05	YES
DIASTOLIC BP	0.24	0.094	NO
FAMILY HISTORY	0.094	0.517	NO
SMOKING	0.06	0.678	NO
ALCOHOL INTAKE	0.1	0.49	NO
WAIST CIRCUMFERENCE	0.663	0.001	YES
TRIGLYCERIDE	0.315	0.026	YES
HIGH DENSITY LIPOPROTEIN	0.323	0.022	YES
FASTING BLOOD SUGAR	0.293	0.039	YES

DISCUSSION

The metabolic syndrome (MS) is a silent epidemic which includes various abnormalities leading to increased cardiovascular morbidity and mortality. The commonly documented metabolic risk factors are dyslipidemia, hypertension, and diabetes. The dyslipidemia includes a combination of lipoprotein abnormalities like reduced level of high-density lipoprotein cholesterol (HDL-C) and increased level of serum triglyceride (TG), apolipoprotein B, and low-density lipoprotein cholesterol (LDL-C). This study, “THE PREVALENCE OF METABOLIC SYNDROME IN YOUNG ACUTE CORONARY SYNDROME PATIENTS” is an observational study done on 50 patients of age < 45 years admitted with acute myocardial infarction in Tirunelveli medical college hospital.

The study population included 50 patients presented with acute myocardial infarction of which 49 patients were male and 1 was female. Among the 50 patients 23 were diagnosed to have metabolic syndrome based on the NCEP ATP III guidelines. Several previous studies have shown that the overall prevalence of metabolic syndrome in Indian population is 31.4%. It was observed that females (48.2%) are more affected than their male counterparts (16.3%). When evaluating the age wise prevalence, it is seen that prevalence increased from 2.9% in those aged 18–30years to 31.0% in those aged 60–69 years in Asians. In urban

India, studies have shown that in coronary artery disease (CAD) patients, the prevalence of MS was reported to be 60.06%.

In the study “Metabolic syndrome in young Asian Indian patients with myocardial infarction” N Ranjith, Rj Pegoraro et al, assessed the prevalence of the metabolic syndrome in young South African Indians (≤ 45 years) with acute myocardial infarction (AMI) using the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) The study population comprised 389patients with acute myocardial infarction . The metabolic syndrome as defined by the NCEP ATP III criteria was found in 235 (60%) patients. Elevated fasting blood glucose was the major NCEP ATPIII determinant present in 86% of individuals. All determinants in definitions were found more frequently inpatients with the metabolic syndrome ($p < 0.001$).

In another recent study “ Prevalence and Predictors of Metabolic Syndrome in Young Asymptomatic Gujarati Population” Sharad R. Jain, Komal H. Shah et al published in 2015 it was observed that prevalence rates of metabolic syndrome were 16.0% in young population (20–40 years). In males it was 21.5% and in females 10.8%. The study also found out that prevalence increased with advanced age as 9.56% of the young population (20–30 years) had Metabolic syndrome, in contrast to the 24.57% in the old (31–40 years).

In our study, the metabolic syndrome, as defined by the NCEP ATP III criteria, was found in 23 patients (46%) of the study population. The fasting blood glucose was the most common NCEP ATP III determinant elevated in patients with or without the metabolic syndrome, about 72%. The prevalence of other components were raised triglyceride levels (50%), low HDL cholesterol levels (40%), increased waist hip ratio (16%) and elevated systolic blood pressure (48%).

The mean age of the sample population was 38.48. Among the 50 patients, 13 were below the age of 35 years, 18 were between 36 to 40 and 19 were having age above 40. The associated risk factors were also assessed. Smoking was present in 32 patients (64%) among the study population where as alcohol consumption was seen in 33 patients (66%).

The fasting blood glucose was the most common NCEP ATP III determinant in patients with or without the metabolic syndrome, about 72%. Among the 23 patients with metabolic syndrome, 22 patients had elevated fasting blood glucose levels and one had normal level. Statistically significant correlation was found between elevated fasting blood glucose levels and metabolic syndrome. The mean fasting blood sugar level was found to be 147.87mg/dl in patients with metabolic syndrome and 116.44 mg/dl in patients without metabolic syndrome. The difference was found to be statistically significant.

Another parameter closely related with metabolic syndrome is triglyceride levels. In this study, raised triglyceride levels was seen in 25 patients (50%). Among the 23 patients with metabolic syndrome, 16 patients had elevated triglyceride levels. The mean triglyceride level was found to be 199.34 mg/dl in patients with metabolic syndrome and 150.59mg/dl in patients without metabolic syndrome. The difference was found to be statistically significant.

CONCLUSION

The prevalence of metabolic syndrome in young patients presented with acute coronary syndrome was found to be around 46%. Among all the components of metabolic syndrome, fasting blood glucose was the commonest component elevated. The prevalence of other components were raised triglyceride levels (50%), low HDL cholesterol levels (40%), increased waist hip ratio (16%) and elevated systolic blood pressure (48%). This high prevalence of metabolic syndrome in young population reinforces the need for a comprehensive non communicable disease prevention and control program. Increasing awareness and early identification of these clusters of risk factors should be emphasized in designing population wide prevention strategies. The major goals are to address both the underlying cause of the syndrome, and also the other cardiovascular risk factors if they persist. The majority of people with metabolic syndrome are overweight and lead a sedentary lifestyle. Therefore, lifestyle modification is needed. Weight reduction usually requires a specifically tailored multifaceted program that includes diet and exercise.

While the conventional definition of metabolic syndrome has not changed much for over a decade, other factors that should be considered, which are supposed to play a role includes C-reactive protein (CRP),

increased intima-media thickness of carotid arteries, and increased pulse wave velocity. When the full spectrum of various aetiological factors and risk markers of CVD risk in metabolic syndrome is uncovered, we can more effectively implement concrete preventive strategies in the community on a wide scale.

1. K. Pandit, S. Goswami, S. Ghosh, P. Mukhopadhyay, and S. Chowdhury, “Metabolic syndrome in South Asians,” *Indian Journal of Endocrinology and Metabolism*, vol. 16, no. 1, pp. 44–55, 2012.

2. M. Das, S. Pal, and A. Ghosh, “Association of metabolic syndrome with obesity measures, metabolic profiles, and intake of dietary fatty acids in people of Asian Indian origin,” *Journal of Cardiovascular Disease Research*, vol. 1, no. 3, pp. 130–135, 2010.

3. C.-E. Tan, S. Ma, D. Wai, S.-K. Chew, and E.-S. Tai, “Can we apply the national cholesterol education program adult treatment panel definition of the metabolic syndrome to Asians?”*Diabetes Care*, vol. 27, no. 5, pp. 1182–1186, 2004.

4. V. Achari, A. K. Thakur, and A. K. Sinha, “The metabolicsyndrome-its prevalence and association with coronary arterydisease in type 2 diabetes,” *Journal, Indian Academy of ClinicalMedicine*, vol. 7, no. 1, pp. 32–38, 2006.

5.Reaven G banting lecture. Role of insulin resustence in human disease. Diabetes 1988;371:595-607

6.World health organisation (1999) definition diagnosis and classification of diabetes mellitus and its complications . part 1 : diagnosis and classification of diabetes mellitus WHO geneva 1999

7. Balkau B , Charles M A. comment on the provisional report from Who consultation. European group for the study of insulin resistence (EGIR). *Diabet med 1999;16;442-443*

8.Grundy SM, Brewer HB Jr, Cleeman JI , Smith SCJr, Lenfant C. Definition of metabolic syndrome ; Report of the national Heart ,Lung, And Blood Institute/ American heart association conference on scientific issues related to definition. *Circulation* 2004*;109:433-438*

9.Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *J Am Med Assoc* 2002; **287**: 356−359.

10.Moller D.E and flier J.S. Mechanisms of disease: Insulin resistence-mechanisms, syndromes and implications. *N Engl J Med 1991;325:938-948*

11. Pi-Sunyer .Metabolic Syndrome In Obesity. Obesity Research 2004 Vol .12

12 Joshi R. Metabolic Syndrome- Emerging Clusters Of Indian Phenotype. *J assos physicians india 2003 ;51:445-446.*

13.Rutledge AC , Adeli K . Fructose And Metabolic Syndrome; Pathophysiology And Molecular Mechanisms. Nutr Rev. 2007 Jun ;65 :S13-23

14.Lu JY Huang KC et al Adiponectin: a biomarker of obesity induced insulin resistencein adipose tissue and beyond. *J biomed sci 2008 sep15(5)565-76*

15.Sakkinen PA, Wahl P, Cushman M, Lewis MR et al. Clustering Of Procoagulation , Inflammation, And Fibrinolysis Variables With Metabolic Factors In Insulin Resistance Syndrome. *Am J Epidemol. 2000 Nov 15;152;897-907*

16.Jilall I , Devaraj S , Adams Huet B, Chen X et al. Increased Cellular And Circulating Biomarkers Of Oxidative Stress In Nascent Metabolic Syndrome.

J Clin Endocrinol Metab 2012 Aug 7

17. Rh Eckel Et Al. *Lancet 2005 365:1415*

18. Harrison's Principles Of Internal Medicine19th Edition

19. Gami AS, Witt BJ, Howard DE et al. Metabolic Syndrome And Risk Of Incident Cardiovascularevents And Death. A Systematic Review And Metaanalysis Of Longitudinal Studies. *J Am Coll Cardiol 2007 ;49: 403-14.*

20. Malik S, Wong ND, Franklin SS et al. Impact Of Metabolic Syndrome On Mortality From Coronary Heart Disease And All Causes In United States adults

Circulation2004 ;110; 1245-50

21. Sutton Tyrrell K, Newman A, Simonsick R et al. Aortic Stiffness Is Associated With Visceral Adiposity in Older Adults Enrolled In Study Of health ageing And Body Composition. *Hypertension 2001;38:429-33*

22. Salomaa V, Riley W, Kark Jd And Folsom A. Non Insulin Dependent Diabetes Mellitus And Fasting Glucose And Insulin Concentrations Are Associated With Arterial Stiffness Indexes. The ARIC Study. *Circulation 1995 : 91; 1432-43*

23. Cull CA, Jensen CC, Retnakaran R, Holman RR et al. Impact Of Metabolic Syndrome On Macrovascular And Microvascular Outcomes In Type 2 Diabetes Mellitus *Circulation 2007116: 2119-26*

24. Lamon BD, Hajjar DP. Inflammation At The Molecular Interface Of Atherogenesis. *The American Journal Of Pathology 2008;175;1253-63*

25. Suzuki T, Hirata K, Elkind MS. Metabolic Syndrome Endothelial Dysfunction And The Risk Of Cardiovascular Events: The Northern Manhattan study. *American Heart Journal 2008:156:405-10*

26. A Festa, D Agostino et al. Chronic Subclinical Inflammation As A Part Of the Insulin Resistance Syndrome; The Insulin Resistance Atherosclerosis Study (IRAS) *Circulation Vol 102pp 42-47 , 2000*

27.Ridker PM, Cushman M, et al. Inflammation , Aspirin, And The Risk Of Cardiovascular Disease In Apparently Healthy Men. *N Engl J Med 1997;336:973-9*

28.Wilson PW, Parise H, Meigs JB et al. Metabolic Syndrome As A Precursor Of Cardiovascular Disease And Type 2 Diabetes Mellitus. *Circulation 2005 Nov 15;112(20): 3066-72*

29. Ingelsson E, Sullivan LM et al. Prevalence And Prognostic Impact Of Subclinical Cardiovascular Disease In Individuals With Metabolic Syndrome And Diabetes. *Diabetes 2007 ;56 :1718-26*

30. Widlansky ME, Gokce N et al 2003 . The Clinical Implications Of Endothelial Dysfunction . *J Am Coll Cardiol 42:1140-60*

31. Massimo Franchini et al. Hemostatic Abnormalities In Endocrine And Metabolic Disorders. *European Journal Of Endocrinology;2010,162:439-51*

32. Maede et al. Haemoststic Function And Ischemic Heart Disease: Principal Results Of The Northwick Partk Heart Study. *Lancet 1986 2:533-37*

33. Rosario Montario And Isabel, Review Article, Chronic Inflammation In Obesity And Metabolic Syndrome. *Mediators Of Inflammation Vol 2010*

34. Misra DP, Dsa S, Sahu PK,. Prevalence Of Inflammatory Markers In Indian Patients With Type 2 Diabetes. *Metabolic Syndrome And Related Disorders 2012*

SL NO.	AGE	SEX	IP. NO	smoking	alcohol consumption	family history	BP	WAIST CIRCUMFERENCE	TG	HDL-C	FBS	T2DM	SHT	DIAGNOSIS	METABOLIC SYNDROME
1	33	M	49620	yes	yes		130/80	94	167	46	110			AWMI	YES
2	30	M	49649		yes		110/80	106	230	36	106			ASMI	YES
3	39	M	50501	yes	yes		110/70	101	100	35	169			IWMI	YES
4	44	M	48621	yes	yes	yes	120/90	86	185	42	109			AWMI	YES
5	45	M	48862	yes			140/100	92	165	41	156	YES	YES	IPWMI	YES
6	30	M	52097	yes	yes		120/80	90	267	45	90			IWMI	
7	43	M	52379	yes	yes		110/70	84	106	42	100			AWMI	
8	32	M	64836				140/100	88	125	33	103			IPWMI	YES
9	41	M	64278	yes	yes		140/100	88	139	37	84			AWMI	
10	35	M	64108				120/70	86	431	24	178	YES		AWMI	YES
11	26	M	66778	yes	yes		110/70	89	188	36	114			AWMI	YES
12	32	M	71049	yes	yes		110/70	73	100	43	127			IPWMI	
13	44	M	73691	yes	yes		30/80	63	108	40	129			AWMI	
14	42	M	73698				120/80	92	129	45	80			ASMI	
15	42	M	78923	yes	yes		110/70	86	91	41	157			IWMI	
16	41	M	79180	yes			130/80	84	125	45	112			AWMI	
17	45	M	79451	yes			130/90	86	350	50	120			AWMI	YES
18	45	M	79654	yes	yes		130/70	76	200	40	149			AWMI	
19	40	M	83709	yes	yes		40/90	91	118	36	357			AWMI	YES
20	30	M	84009	yes	yes	yes	110/70	92	94	40	97			AWMI	
21	37	M	84857		yes		110/70	75	110	46	170	YES		AWMI	
22	30	M	66117	yes	yes		160/100	96	191	40	150			IWMI	YES
23	35	M	4961	yes	yes	yes	110/80	85	345	31	65			ASMI	
24	41	M	2473			yes	190/150	92	142	46	98			AWMI	
25	37	M	2206	yes	yes		140/100	94	350	50	110			AWMI	YES
26	40	M	1549	yes	yes		110/90	86	210	38	96			IWMI	
27	44	M	6658		yes		140/100	85	114	35	127			AWMI	YES
28	40	M	7137	yes	yes		130/90	74	100	45	98			AWMI	
29	31	M	7559				140/90	86	125	45	220	YES	YES	ASMI	
30	40	M	7869	yes	yes		130/80	78	96	46	118			IWMI	

31	37	M	7892		yes		140/100	92	145	36	120			AWMI	YES
32	30	M	37682	yes	yes		20/80	94	170	40	110			AWMI	YES
33	45	M	37602				110/80	92	281	36	161	YES		AWMI	YES
34	40	M	30159	yes			100/70	80	188	42	72			ASMI	
35	39	M	29716	yes	yes		100/60	89	170	44	154			AWMI	
36	45	M	23530	yes	yes		150/100	88	350	50	336	YES		AWMI	YES
37	40	M	21633	yes	yes		160/100	92	119	36	177	YES	YES	AWMI	YES
38	42	M	21605	yes	yes		120/80	94	118	34	120		YES	AWMI	YES
39	40	M	11701				100/60	96	182	36	137			AWMI IWMI	YES
40	43	M	12265	yes	yes		160/90	86	110	44	124			AWMI	
41	38	M	12365		yes	yes	110/70	86	176	46	126			AWMI	
42	41	F	13658	yes			110/70	88	143	42	110			AWMI	
43	38	M	13566				120/80	84	186	34	98			AWMI	
44	39	M	13865		yes		110/80	88	142	38	118			IWMI	
45	39	M	14586	yes	yes		110/80	82	144	46	162			AWMI	
46	44	M	14569			yes	140/100	92	165	35	110			AWMI	YES
47	41	M	14899		yes		110/90	88	142	43	100			AWMI	
48	34	M	13548				140/100	96	165	46	123			IWMI	YES
49	39	M	14758				120/90	84	178	41	90			AWMI	
50	36	M	15487	yes			140/90	93	176	34	98			AWMI	YES

THE PREVALENCE OF METABOLIC SYNDROME IN YOUNG ACUTE CORONARY SYNDROME PATIENTS

PATIENT DETAILS

NAME: AGE: SEX:

IP.NO: CONTACT NO.:

DOA: DOD:

ADDRESS: OCCUPATION:

COMORBIDITIES:

DM	SHT	CAD	PTB	BA		

ADDICTIONS : SMOKING: ALCHOHOL INTAKE:
OTHERS IF ANY:

FAMILY HISTORY IF ANY:

PRESENTING FEATURES:

GENERAL EXAMINATION

PULSE: BP: SPO2: JVP:

PALLOR	ICTERUS	CYANOSIS	CLUBBING	LYMPHNODE	ODEMA

DYSLIPIDEMIA MARKERS IF ANY

CXR PA VIEW:

HEIGHT (cm)	
WEIGHT(kg)	
WAIST CIRCUMFERENCE (cm)	

ECG:

TOTAL CHOLESTEROL	
TRIGLYCERIDES	
HDL	
LDL	
VLDL	

ECHO:

RBS	
FBS	
PPBS	
B.UREA	
S cr	
S Na	
S.K	

"A STUDY OF CLINICAL PROFILE OF DILATED CARDIOMYOPATHY IN CORRELATION WITH ECG AND ECHOCARDIOGRAPHY."

NEED FOR STUDY:

Cardiomyopathy is a primary disorder of the heart muscle that causes abnormal myocardial performance and is not the result of disease or dysfunction of other cardiac structures. The dominant feature is a direct involvement of the heart muscle itself. They are distinctive because they are not the result of pericardial, valvular or congenital diseases. The prevalence of heart failure is about 1 to 1.5% of the adult population. The mortality and morbidity remain high (median survival of 1.7 years for men and 3.2 years for women). Dilated cardiomyopathy is an important cause of heart failure and accounts for up to 25% of all cases of CHF

AIMS AND OBJECTIVES OF THE STUDY :

1.To study the clinical profile of patients with dilated cardiomyopathy

2.To study the electrocardiographic and echocardiographic profile of these patients

METHODS OF COLLECTION OF DATA:

1.Information will be collected through a pre tested and structured Performa for each patient.

2.The study will be carried out on patients presenting with clinical features and ECG & 2D Echocardiographic findings of Dilated cardiomyopathy.

3.In all the selected patients detailed history and physical examination will be noted. Every patient will be subjected to 12 lead ECG & Echocardiography.

ABBREVIATIONS

MS	-	Metabolic Syndrome
IR	-	Insulin Resistance
IGT	-	Impaired Glucose Tolerance
DM	-	Diabetes Mellitus
CVD	-	Cardiovascular Disease
HDL	-	High-Density Lipoprotein
VLDL	-	TG Very-Low-Density Lipoprotein–Triglyceride
TG	-	Triglyceride
LDL Low	-	Density Lipoproteins
WHO	-	World Health Organisation
EGIR	-	European Group For Study Of Insulin Resistance
NCEP:ATPIII	-	National Cholesterol Education Program And Adult Treatment Panel III
IRS	-	Insulin Receptor Substrate
TNFa	-	Tumor Necrosis Factor
PAI-1	-	Plasminogen Activator Inhibitor
PI3K	-	Phosphatidylinositol -3 Kinase
MAPK	-	Mitogenic Or Mitogen – Activated Protein Kinase
NAFLD	-	Nonalcoholic Fatty Liver Disease
TZD	-	Thiazolidinediones
ACE	-	Angiotensin-Converting Enzyme